The Management of Major Depressive Disorder in Cancer Patients: A Randomised Trial

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Declaration: I confirm that the work contained in this Thesis is my own original work.

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CONCLUSION

Chapter 13 Review of Aims and Hypotheses 195

Chapter 14 Future Research 200

APPENDICES

Appendix A Treatment Manual 234

Appendix B Depression Severity Measure - PHQ-9 277

Appendix C Quality Control Manual 278

Appendix D Self-report Trial Outcome Measures 296

Appendix E Data Collection Form & Data Definitions 304

Appendix F Patient Information and Consent Forms 306

INTRODUCTION

Chapter 1: Background

Chapter 2: A Nurse-Delivered Multiple Modality Approach to the Management of Major Depressive Disorder in Cancer Patients

Chapter 3: Aims and Hypotheses

CHAPTER 1: BACKGROUND

Sections

Major Depressive Disorder
- Definition & diagnosis
- Prevalence

Major Depressive Disorder in Cancer
- Definition & diagnosis in patients with cancer
- Prevalence

Management of Depression in Primary Care
- Recognition
  - *Screening*
- Treatment
  - *Antidepressants*
  - *Psychological treatments*
  - *Combined treatments*
  - *Collaborative models of depression management*

Management of Depression Comorbid with Chronic Illness including Cancer
- Recognition
  - *Screening*
- Treatment
  - *Antidepressants*
  - *Psychological treatments*
  - *Combined treatments*
  - *Collaborative models of depression management*

List of Tables

Table 1.1: Prevalence of Major Depressive Disorder using a DSM criteria-based structured clinical interview

The search terms for the literature review included cancer, depressive disorder, prevalence, treatment, psychological therapy, antidepressant medication, multi-component intervention, nurse-delivered. A number of electronic databases were used for searching the literature. These were accessed through e-library NHS and Athens. The databases included a range of sources including medical, nursing, Allied Health Professional and generic journals. A thorough review was undertaken of the literature concerning the prevalence and treatment of depression in both cancer and non-cancer populations.

Cancer and depression are two of the most common causes of death and disability worldwide (Murray and Lopez 1996, WHO 2004).

As more effective anti-cancer treatments emerge the prognosis for patients with cancer is constantly improving resulting in a large number of patients living with the disease for significant periods of time. Cancer for some patients has therefore become a chronic disease. The treatment of chronic disease focuses primarily on symptom management and requires a co-ordinated approach to care such as that described in the chronic illness care model developed by Wagner (1998). For cancer patients, symptom management is the primary therapy after surgery, chemotherapy, radiation, hormonal or biological therapies, either as a transition back to follow-up by primary care services or as a bridge to end-of-life care. Symptom management is the diagnosis, treatment and monitoring of a symptom and is common to all types of cancer and all stages of disease. The main symptoms associated with cancer are pain, fatigue and depression.

MAJOR DEPRESSIVE DISORDER

Depression is becoming one of the most pressing public health problems in the developed world and is ranked as the fourth leading cause of disease burden globally (Ustun et al 2004). The more severe form of depression is called Major Depressive Disorder (MDD). A US epidemiological study showed that the diagnosis of MDD was associated with significant functional impairment and almost half of people with MDD had suicidal ideation, making MDD a serious personal and public health problem (Hasin et al 2005). Projections suggest that by 2020, in the US, MDD will be responsible for a larger burden of disease than any other illness (Greenberg et al 2003).

Definition and diagnosis

MDD is characterised by persistent low mood and/or anhedonia with additional functional impairment and somatic symptoms. It is diagnosed when at least 2 weeks of persistent depressed mood or anhedonia are present, accompanied by changes from normal functioning in a total of at least four or more (or at least three if they have both depressed mood and anhedonia) of the remaining DSMIV (Diagnostic and Statistical Manual for Mental Disorders Fourth Edition, American Psychiatric Association 1994) symptoms of major depression (sleep disorder, appetite change, fatigue, psychomotor retardation and/or agitation, low self-esteem and/or guilt, poor concentration and/or indecisiveness and thoughts of suicide and/or suicidal ideation during the current episode).

Prevalence

The point prevalence of MDD has been reported to be 5.3% in the USA (Hasin et al 2005) and 7% in the UK (Ayuso-Mateos et al 2001).

MAJOR DEPRESSIVE DISORDER IN CANCER

MDD comorbid with chronic illness such as cancer demands attention as it is a major determinant of quality of life, is associated with non-adherence to treatment (DiMatteo et al 2000; Ciechanowski et al 2000; Lin et al 2004), with greater functional impairment or disability (Sullivan et al 1997; Unutzer et al 2000; Von Korff et al 2005), with increased physical symptom reporting, with increased medical costs (Chochinov 2001; Musselman et al 2001; Katon and Ciechanowski 2002) and is associated with suicide (Cavanagh et al 2003; Chochinov et al 1997 & 1998). There is also recent published data of a large study of more than 10,000 patients over 8 years providing evidence that the coexistence of cancer and depression (although not specifically MDD) is associated with an increased risk of death from all causes (Onitilo et al 2006).

Definition and diagnosis in patients with cancer

In cancer patients, although depressive symptoms are often considered an understandable reaction to cancer, the diagnosis of MDD follows the same DSMIV criteria as described above.

However there is some controversy concerning the use of DSM criteria in the diagnosis of depression comorbid with physical illness. Firstly, although DSM criteria are considered the gold standard, they were developed and validated on populations without physical illness therefore casting doubt as to whether they actually are the gold standard for all patients, particularly those with significant medical illness. Secondly, many depressive symptoms are similar to those of the medical illness itself, presenting a diagnostic challenge.

In cancer, and specifically in advanced disease, many of the vegetative depressive symptoms such as appetite loss, weight loss, insomnia, loss of energy and loss of interest are common to both illnesses. The controversy is centred around determining the source of the physical symptoms. So, in an attempt to identify an accurate method of assessing depression in medically ill patients, in particular cancer patients, researchers have proposed four different approaches: inclusive, aetiologic, substitutive and exclusive (Cohen-Cole et al 1993; McDaniel et al 2000). The inclusive approach uses all the symptoms of depression, regardless of whether they may or may not be secondary to a physical illness (Rifkin et al 1985), potentially resulting in over-diagnosis. In contrast the aetiologic approach counts a symptom only if it is clearly not caused by the physical illness (Rodin et al 1991), resulting in variability as it relies on the clinician diagnosing the depression being familiar with the accompanying medical illness. An approach designed to avoid confusion over the cause of symptoms, is the substitutive approach which allows physical symptoms related to the medical illness in question to be replaced with cognitive symptoms such as indecisiveness, hopelessness and pessimism. For cancer, Endicott provided

specific modified criteria (Endicott 1984) substituting change in weight or appetite, sleep disturbance, loss of energy or fatigue and difficulty in thinking or concentration with depressed appearance, social withdrawal or decreased talkativeness, brooding, self pity or pessimism and lack of reactivity in situations that would normally be pleasant. However a study comparing the Endicott modification against the inclusive approach (Ciaramella and Poli 2001) found that the prevalence rate dropped from 49% to 29%. The final approach, the exclusive approach proposed by researchers at the Sloan-Kettering Cancer Institute (Bukberg et al 1984; Plumb and Holland 1981) eliminates two common symptoms of depression (fatigue and appetite/weight changes) using only the other symptoms. This approach has been shown to lose sensitivity, in other words it risks missing cases (Kathol et al 1990).

However, the method used may not be as important as previously thought. A recent study of the validity of DSMIV depression criteria in medical co-morbidity (Simon and Von Korff 2006) found only limited evidence that fatigue, change in weight or appetite, psychomotor agitation/retardation and sleep disturbance are less valid indicators of depression in patients with chronic medical conditions.

Prevalence

There is evidence that the relative risk of psychiatric disorder is higher in people with medical disorders and chronic illness than in the normal population (Rapp et al 1988; Lustman et al 1998). To put into context the prevalence of MDD in cancer patients it is important to review the reported prevalence in other medical illnesses. The percentage of patients meeting the DSMIV criteria for MDD has been reported to be

15-20% in heart disease (Krishnan et al 2005), 12-18% in diabetes (Anderson et al 2001; Katon et al 2004a) and 50% in chronic asthma or chronic lung disease (Goldney et al 2003; Mikkelsen et al 2004). Prevalence rates for MDD in cancer patients range from 1% to 40% (see table 1.1). Even though these studies have used standardised DSM criteria for diagnosis, there is a wide range of reported rates. There could be a number of explanations for this variability. Firstly, the majority of studies had a high rate of excluded patients which assumes that those not interviewed would have similar rates of depression and secondly, most studies assessed MDD in hospitalised patients where its prevalence is known to be higher. Overall the majority have used small samples of insufficient size to obtain accurate prevalence estimates in a range of settings (inpatients and outpatients) and in a range of cancer types and disease stages (curative and palliative).

Table 1.1: Prevalence of Major Depressive Disorder using a DSM criteria-based structured clinical interview

Author (year)	Population/setting	Sample size	MDD prevalence
Akechi et al 2001	Lung/ns	129	4.7%
Akechi et al 2004	Mixed advanced cancers/IP	209	6.7-11.8%
Alexander et al1993	Mixed/IP	60	13%
Aragona et al 1996	Breast/ns	85	2%
Berard et al 1998	Breast & lymphoma/OP	100	19%
Breitbart et al 2000	Mixed advanced cancers/IP	92	16%
Bukberg et al 1984	Mixed/IP	62	24%
Chochinov et al 1997	Mixed advanced cancers/IP	200	7.6%
Ciaramella and Poli 2001	Mixed advanced cancers/OP (referrals to pain and palliative care clinic)	100	28%
Colon et al 1991	Leukaemia/IP	100	1%
Constantini et al 1999	Breast/OP	132	9.8%
Derogatis et al 1983	Mixed/IP&OP	215	6%
Ell et al 2005	Breast & gynaecological/OP	472	24%
Evans et al 1986	Gynaecological/IP	83	23%
Ginsberg et al 1995	Newly diagnosed lung/ns	52	2%
Golden et al 1991	Gynaecological/IP	65	23%
Grandi et al 1987	Breast/IP	18	22.2%
Hall et al 1999	Breast/OP	269	37.2%
Hosaka and Aoky 1996	Mixed/IP	65	21.5%
Ibbotson et al 1994	Mixed/OP	513	17%**
Joffe et al 1996	Gastric & lymphoma/IP	21	33%

Kadan-Lottick et al 2005	Mixed advanced cancers/OP	251	6.8%
Kathol et al 1990	Mixed/ns	152	38%
Katz et al 2004	Head and neck/OP	60	5%
Kawase et al 2006	Mixed/ Radiotherapy OP	282	8.5%
Kissane et al 2004	Breast/OP	503	8.3%
Kugaya et al 2000	Newly diagnosed head and neck/ns	107	3.7%
Love et al 2002	Breast/OP	303	9.6%
Love et al 2004	Metastatic Breast/ns	227	7%
Massie and Holland 1987	Mixed cancers/IP	546	9%
Morton et al 1984	Head and neck male/OP	48	39.6%
Okamura et al 2000	Breast/ns	55	7%
Payne et al 1999	Breast/OP	31	0%
Razavi et al 1990	Mixed cancers/IP	128	26%
Razavi et al 1992	Lymphoma/OP	117	6.8%**
Sharpe et al 2004a	Mixed cancers/OP	3938	7.8%
Sneeuw et al 1993	Breast/ns	1112	5.4%
Walker et al (2007 in press)	Mixed cancers/OP	361	8.3%

*OP=outpatients; IP=inpatients; ns=not specified
**MDD and generalised anxiety disorder combined

In this thesis I intend to focus on the management of MDD comorbid with cancer. However, because the literature on depression related to cancer is limited, I have chosen to review and relate to some of the key literature on the management of MDD in primary care and of MDD comorbid with chronic illnesses other than cancer.

MANAGEMENT OF DEPRESSION IN PRIMARY CARE

Ninety percent of cases of 'detected' depression are treated in primary care, where depression is the third most common reason for consultation. The two most important barriers to effective depression management are under-recognition (30% remain undetected) and under-treatment (>50% are untreated), (Hays et al 1995).

Recognition

Screening

Lack of recognition of depression in both primary care and medically ill patients is well documented (Schulberg et al 1985; Neilsen and Williams 1980; Wells et al 1989). Depression screening has therefore been recommended for all medical populations (Wright 1994, Pignone et al 2002). However, a systematic review found that increased recognition of depression did not necessarily equate with any benefit in outcome for disorders managed in non-psychiatric settings (Gilbody et al 2001). This suggests that unless there is a coherent management plan for patients identified with depression, screening is of little benefit.

Treatment

However, once detected, the three most commonly used treatment modalities for MDD are antidepressant medication, psychological therapies and combined treatments.

Antidepressants

There is good evidence for the efficacy of antidepressant drugs in non-cancer populations (Joffe et al 1996; Butler et al 2005; Krishnan 2005) and of remission of depressive symptoms (Trivedi et al 2006). However, in practice only a small proportion of patients achieve a therapeutic dose either because the GP did not increase the dose (George et al 2000) or because of poor therapy adherence by the patient (Lin et al 1995).

Psychological treatments

There is also evidence for the efficacy of psychological therapies (Butler et al 2005): for cognitive therapy (Casacalenda et al 2002); interpersonal therapy (de Mello 2005); non-directive counselling (although only short-term efficacy over usual care) (Bower et al 2003); and problem solving therapy (PST) (Mynors-Wallis et al 1995) in treating MDD in non-medically ill populations.

Combined treatments

Interventions that combine pharmacotherapy and psychotherapy have been found to substantially improve patient outcomes for MDD in a number of non-cancer populations (Friedman et al 2004; Katon et al 2004b; Pampallona et al 2004; Callahan et al 2005). In primary care, a patient educational drug compliance enhancing programme provided by GPs for patients with MDD was superior to usual care in achieving a treatment response (Akerblad et al 2003) but the treatment effect was much smaller than that achieved by more complex interventions. Another similar trial of a drug compliance enhancing programme consisting of a brief

psychosocial intervention delivered by nurse found a significantly superior effect on drug adherence compared to usual management with tricyclic antidepressant medication, but clinical effect in terms of treatment response was only seen in the subset who were also taking 75mg or more of the tricyclic drug (Peveler et al 1999).

The better outcome in both depression and medication adherence achieved by combined treatments was supported by Gilbody et al (2003) in a systematic review which found that almost all trials of depression management using at least two or combined depression management strategies had positive results in their primary outcomes and that the most successful interventions combined multiple strategies such as those specified in the definition of collaborative care models of depression management.

Collaborative models of depression management

Collaborative models in primary care, also called depression management programmes (DMP) or collaborative care programmes, contain the following elements: evidence-based protocols for treatment; structured collaboration between primary care providers and mental health specialists; active monitoring of adherence to treatment and of outcomes; and in some cases structured programmes of psychotherapy (Simon 2006). This type of model is based on the concept of collaborative management in chronic illness, that is care that strengthens and supports self-care while assuring that effective medical, preventive and health maintenance interventions take place (Von Korff et al 1997).

At the time of planning my research there had been a small number of large well-designed randomised controlled trials (RCT) of such interventions for depression in primary care. Early leading studies using patient education strategies and treatment interventions delivered by a range of primary care health workers (GPs, psychologists, psychiatrists and nurses) were conducted by a research group in Seattle led by Professor Wayne Katon.

In 1995 Katon and colleagues published results of a large randomised controlled trial of a multifaceted intervention for patients with major and minor depression (Katon et al 1995) consisting of collaborative management by the primary care physician and a consulting psychiatrist, intensive patient education, and monitoring of antidepressant medication. The intervention achieved a statistically significant improvement in depressive outcomes for patients with major, but not minor, depression over usual care. In 1996 the Group published results of a second RCT of a similar intervention but with the addition of a psychological intervention delivered by a psychologist integrated into the primary care practice (Katon et al 1996). This also showed a significantly improved depression outcome for patients with MDD, with a treatment effect of a similar order of magnitude to the previous trial. A further development of the collaborative care model proposed by Katon's research group was a stepped approach whereby patients not responding to initial conventional treatment would receive enhanced care, comprising patient education, two sessions with a primary care based psychiatrist, nurse case management and collaborative management by the psychiatrist and GP. This model was tested against usual care in patients with

persistent MDD and was found to be efficacious in terms of depressive outcomes over usual care (Katon et al 1999).

The collaborative care model was extended to specific patient populations by Katzelnick and colleagues in Harvard University, Boston, and its efficacy in the management of MDD in high utilisers of medical care tested in an RCT across a large number of primary care practices. The model, a depression management programme, consisted of GP education, the provision of antidepressant medication prescribing guidelines, patient education and case management by a primary care mental health worker. Results published in 2000 showed superior outcomes in depressive outcomes for patients receiving the new intervention compared to usual care (Katzelnick et al 2000).

In the same year a research group in the University of California (Hunkeler et al 2000) published results of a trial of the collaborative care model for the management of MDD and dysthymia. This model, 'nurse telehealthcare' extended the nurse's role in case management to include both drug adherence monitoring and support in the form of problem-solving and activity scheduling by phone, together with GP prescribed antidepressant medication. Although the intervention was superior in efficacy over usual care for depressive symptom outcomes, it did not alter adherence to medication. This was the first trial to provide evidence for the efficacy of phone-delivered depression treatment, thus broadening its accessibility.

Although not in phone-delivered format, the same research group also investigated the dissemination of a depression management programme in a large RCT in forty-six primary care practices with 1356 patients with MDD comparing a DPM using nurse case managers to provide treatment monitoring, patient education and activation and psychotherapist-delivered cognitive behavioural therapy (CBT) with usual care. This trial demonstrated improvement in depression outcomes in patients who received the DPM both at six and twelve months but more-over that dissemination of guidelines for such a DPM to routine practice is effective (Wells et al 2000).

At about the same time, a group from the University of Colorado were developing and testing a model for MDD in primary care designed to follow the principles of chronic disease management, so delivering 'on-going' care up to twenty-four months with the objective of sustaining or increasing improvement, given that the emerging evidence at that time was that the initial benefits from collaborative care models for depression were not sustained beyond a year (Lin et al 1999). The model included GP prescribed antidepressant medication plus nurse-delivered patient education, and algorithm-guided support and treatment monitoring from baseline to seven months, then nurse case management of structured follow-up phone calls between seven and twenty-four months. The intervention increased response rates significantly compared with usual care at six months (Rost et al 2001) and long-term remission rates by a third at twenty-four months (Rost et al 2002). The results of this trial suggested that a model with structured monitoring beyond the initial phase of

intensive treatment was an important factor in the maintenance of patient improvement.

In 2002, the Seattle group published results of the largest trial to date of collaborative care, the Impact Trial, applying the model to older patients with MDD and multiple medical conditions (Unutzer et al 2002) and comparing it with usual care in an RCT of 1801 patients in eighteen primary care clinics. The model involved a depression care manager (nurse or psychologist) who delivered patient education in the form of a short educational video-tape and booklet, prepared a treatment plan, monitored treatment response using a structured assessment tool, managed the patient's antidepressant regimen alongside their GP and/or gave 6-8 sessions of problem solving therapy (PST). The benefit over usual care was significant and clinically substantial at twelve months with persistent long term benefits at two years reported recently by Hunkeler et al (2006).

In 2003, a collaborative group from the UK, Seattle and Santiago published results of a stepped care model using nurse or social worker-delivered group psycho-education and case management with a structured programme of pharmacotherapy for those with severe or persistent depression for the management of MDD in a population of low-income women in Chile (Araya et al 2003). The trial found a large treatment effect compared to usual care.

However, not all trials have produced positive results. A primary care study of MDD, dysthymia and partially remitting MDD comparing collaborative care management

with nurse case management of patient monitoring, treatment planning, and care co-ordination with notification to GPs regarding diagnosis (Swindle et al 2003) showed no significant differences at three and twelve months compared with usual care.

In conclusion, results from the research available at the start of my trial and a systematic evaluation of collaborative models of depression management conducted by Gilbody and colleagues in 2003 just before the start of the trial, suggested that a combination of antidepressants, brief psychological treatments, and case management with 'maintenance care' beyond the initial intensive treatment phase were important elements of an efficacious model of depression management and that nurse involvement in combined treatments and collaborative models of depression management in primary care varying from low intensity, such as providing brief patient education and medication counselling (Peveler et al 1999), to telephone support (Hunkeler et al 2000), to nurse case management (Katon et al 1999, Wells et al 2000, Rost et al 2002, Araya et al 2003) could be an effective method of delivery of such models.

Since starting the trial, one further large primary care trial of collaborative depression care for patients with moderate to severe depression starting antidepressant treatment has been published by the Seattle group (Simon et al 2004). In this trial three interventions were compared: a telephone-based programme of medication monitoring and care co-ordination; the telephone-based programme with additional structured 8-session depression-specific CBT delivered by psychotherapists over the phone; and usual pharmacotherapy. No significant benefits in depression outcomes

were found by adding the telephone-based medication monitoring programme to usual pharmacotherapy, nor by adding a brief psychotherapy to usual pharmacotherapy. However, a combination of all three interventions (the brief psychotherapy, the telephone-based monitoring programme and usual pharmacotherapy) produced significant differences in depressive outcomes when compared to usual pharmacotherapy alone. This trial suggested that a multi-component intervention may be a contributing factor to overall efficacy of a collaborative care model.

In addition to the trial described above, three systematic evaluations of collaborative models of depression management have been published since the start of the trial, a meta-analysis of twenty-four RCTs published up to 2001 (Badamgarav et al 2003), a meta-analysis of ten American RCTs published up to 2002 (Neumeyer-Gromen et al 2004) and more recently a meta-analysis of thirty-seven RCTs published up to the start of 2006 by Gilbody et al (2006). All three evaluations have confirmed the efficacy of collaborative care models for depression management in primary care with Gilbody's group providing evidence of longer-term benefit for up to five years. It seems therefore that the evidence for the efficacy and effectiveness of collaborative care models for the management of MDD in primary care is well established. However, evidence-based strategies for managing MDD in chronic illness or cancer are less clear.

MANAGEMENT OF DEPRESSION COMORBID WITH CHRONIC ILLNESS INCLUDING CANCER

Recognition

Depression in cancer patients is under-recognised (Passik et al 1998; McDonald et al 1999; Fallowfield et al 2001). The reason for this is complex. Oncologists, and patients too, may be focussed on the medical management of the cancer. Also health care professionals working in non-psychiatric settings may be unfamiliar with the symptoms of depression, particularly as the somatic symptoms can be common to both illnesses. Another reason frequently put forward is that clinicians may dismiss depressive symptoms on the assumption that all cancer patients are 'understandably depressed'. Clinicians may also be hesitant to elicit patients' concerns for fear of upsetting the patient further or may avoid discussing distressing issues because of their own discomfort (Goldman et al 1999). In addition to this is the lack of familiarity with, and availability of, treatment options. Fallowfield and colleagues (2001) in a large study of the recognition of psychiatric morbidity by doctors in patients with cancer showed that doctors misclassify over a third of patients. Patients may also avoid disclosing depressive symptoms because of the associated stigma of the illness (Maguire 1985; Valente et al 1994) and of the treatment (Von Korff et al 2001) or simply that not all patients want their depression treated (Sharpe et al 2004b). Our own research in a sample of 150 cancer patients with MDD (Sharpe et al 2004a) showed that only half had discussed their low mood with their GP.

Screening

Self-report screening measures commonly used in the cancer population include the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) originally designed to detect symptoms of depression and anxiety in patients attending medical outpatient clinics and found to be valid and reliable as a screening instrument (Bjelland et al 2002). In a cancer population, a total score of 15 or above on the HADS scale was reported by Ibbotson et al (1994) to be the best cut-off for identifying patients likely to have a diagnosis of interview-defined depressive or anxiety disorder. Our own research at a HADS total score cut off of 14/15 gave a sensitivity of 0.87 (95% C.I. 0.70-0.95), a specificity of 0.85 (95% C.I .0.81 – 0.89) and a positive predictive value of 0.35 and was considered optimal (Walker et al in press), thus offering 85% accuracy when compared against the MDD section of the Structured Clinical Interview (SCID) for DSMIV (First et al 1999).

Given that doctors' recognition of patient distress is poor and that no screening approach can replace a thorough diagnostic assessment, screening can serve as a resource efficient method of identifying patients requiring further assessment and treatment (Cull et al 2001). However it is not clear from the evidence to date what treatment is effective for MDD in patients with co-morbid chronic illness or cancer.

Treatment

The current treatment for depression in cancer patients is largely derived from evidence-based treatments in the medically ill population as there are no published RCTs to date of effective interventions for MDD in cancer patients. In practice the

management of MDD in cancer patients is often suboptimal. Very few cancer patients with MDD receive effective treatment. A UK survey of 150 cancer patients with MDD showed that 85% were not receiving any appropriate evidence-based treatment for their depression (Sharpe et al 2004a). This is because of a failure to detect it (Fallowfield et al 2001), to deliver appropriate treatment, to monitor progress and to adjust treatment according to response (Von Korff et al 2001; Greenberg 2004; Sharpe et al 2004a) or simply because their physicians tend to attribute their depression to their cancer and/or advancing disease.

Antidepressants

Approximately two thirds of patients who have both cancer and MDD do not receive specific antidepressant treatment (Sharpe et al 2004a).

However, there is emerging evidence for the efficacy of antidepressant drugs in cancer populations (Razavi et al 1996; Musselman et al 2001; Fisch et al 2003; Morrow et al 2003; Roscoe et al 2005) as detailed in a recent systematic review by Williams and Dale (2006).

Psychological treatments

Although there have been no recent meta-analyses of psychological treatment trials specifically for depression in cancer patients, a meta-analysis of RCTs in 1995 (Meyer and Mark 1995) found very little evidence from well-designed RCTs to support the efficacy of psychological therapies in treating depression in cancer populations. However, of the individual trials published after this, cognitive therapy

(Evans and Connis 1995; Edelman et al 1999; Antoni et al 2001; Kuijer et al 2004), PST (Nezu et al 2003), and supportive-expressive group therapy (Classen et al 2001) have been shown to be efficacious.

Combined treatments

There have been no published RCTs of combined treatments for the management of MDD in cancer patients.

Collaborative models of depression management

There have also been no published RCTs of multi-component interventions or collaborative care models for managing MDD in cancer patients and only one major trial of a collaborative care model for the management of depression in patients with chronic illness published after the start of the trial described in this thesis. This was a trial of a collaborative care model in a primary care setting using nurse-delivered brief PST for the treatment of patients with MDD and diabetes, the results of which found it to be superior in terms of depressive outcomes over usual care but in its effect on glycaemic control (Katon et al 2004b).

Although providing only preliminary evidence of efficacy, Dwight-Johnson and colleagues (2005) in Los Angeles have conducted a small pilot RCT of a collaborative model for the management of MDD using social workers to deliver PST in low-income female Latina cancer patients. Although this was a small study, its treatment effect was significant and substantial and provides further evidence of the potential efficacy of such models in cancer populations.

In summary, no trials of depression management in chronic illness or in cancer had been published at the time of starting my trial. Given that a small but robust body of research had been conducted prior to the start of the trial that had proven the efficacy and effectiveness of multi-component interventions for the management of MDD in primary care, and that my preliminary pilot work had found some promising results in a cancer patient population (discussed briefly in the next chapter), it seemed logical to further develop a model informed by the pilot work and test this model formally for its efficacy compared to usual depression management in an RCT.

CHAPTER 2:

A NURSE-DELIVERED MULTIPLE MODALITY APPROACH TO THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN CANCER PATIENTS

In 1999, I designed a multi-component, cancer nurse-delivered intervention collaboratively with Professor Michael Sharpe and tested it in a small non-randomised matched group design pilot study to perform a preliminary evaluation of its feasibility and efficacy in the treatment of MDD in cancer patients, the results of which were published in 2004 (Sharpe et al 2004b). Thirty patients were allocated to usual care and thirty to usual care plus an additional intervention which comprised nurse-delivered patient education and seven sessions of PST, optional GP-prescribed antidepressant medication and nurse case management including medication adherence monitoring and co-ordination of care. The nurse received weekly supervision from the trial psychiatrist. The results of the trial found a statistically significant reduction in both self-rated and interview-based outcomes at three months which were largely maintained at six months. For the primary outcome at six months, 38.5% (95% Confidence Intervals 5.4 to 57%) fewer patients in the additional intervention group still met the diagnosis-based criteria for MDD.

The challenges this role present to nurses were described in a paper published in 2004 (Strong et al 2004). The conclusion was that working with distressed cancer patients could be burdensome without adequate clinical supervision and that integrating a mental health intervention into a secondary care service while relating to primary care was a difficult part of the role.

In summary, results of the pilot study suggested that not only was the intervention promising in terms of its efficacy but that it was feasible to use nurses to deliver it and that it was acceptable to patients and their health care team.

However, while the pilot study found encouraging results, non-randomised comparisons can over-estimate the differences between treatments. Therefore, a randomised comparison was needed, with a bigger sample size to obtain a more precise estimate of its efficacy.

A randomised design in a clinical study ensures that each patient has the same probability of being allocated to each treatment using the play of chance and that the allocation is not predictable by the patient or treating physician thereby allowing a valid basis for comparison of treatments, by minimising biases from known and unknown confounders (Friedman et al 1998). A randomised controlled clinical trial is therefore a rigorous planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients with a given medical condition allowing inferences about the efficacy of an intervention to be made in the population of patients to whom it refers (Pocock 1983).

CHAPTER 3: AIMS AND HYPOTHESES

Sections

Aims

Hypotheses for RCT

Aims:

The overall aim was to improve the management of depression in cancer patients.

The specific objective was to:

1. Test the efficacy of this intervention model for the treatment of MDD in cancer patients of mixed diagnoses in a randomised controlled trial by comparing usual care with usual care plus the nurse-delivered, psychiatrist-supervised multi-component intervention by:
    a. Measuring the primary outcome of trial participants at 3 and 6 months
    b. Measuring other outcomes at 3 and 6 months, specifically:
        i. clinically relevant response to treatment and remission of depressive symptoms
        ii. anxiety, physical functioning, coping, problem-solving ability and satisfaction with treatment
        iii. the association between improvement in depression scores and aspects of confidence, coping and support
        iv. the extent to which baseline factors predict a good outcome at 3 months (although this was not part of the pre-specified statistical analysis plan).

Hypotheses for RCT:

The design of this study was intended to address the stated hypothesis: *Usual care plus a nurse-delivered, psychiatrist-supervised multi-component treatment intervention reduces symptoms of major depressive disorder in patients with cancer to a greater extent than usual care alone.*

Subsidiary hypotheses:

1. The additional nurse intervention will improve outcome by a) increasing the patient's confidence to cope with concerns and b) increasing the patient's coping ability by teaching them problem solving skills to tackle their concerns and c) increasing their access to and use of social support

2. At 6 month follow-up, patients treated with the additional nurse-delivered intervention will maintain the benefit and have benefit superior to those patients who were allocated to usual care only

METHODS

Chapter 4: The Design of the Study

Chapter 5: Analysis of Data and Statistical Power

CHAPTER 4: THE DESIGN OF THE STUDY

Sections

Design

The patient sample
- Population, number and source of subjects
  - *Inclusion criteria*
  - *Exclusion criteria*

The procedure
- Depression screening
- Baseline research assessment
- The Trial
- Randomisation
  - *Justification for randomisation by minimisation*
- The randomisation procedure
  - *Justification for minimisation factors*
- Trial outcome assessments
- The treatment evaluated in the trial
  - *Modification of the trial treatment*
- Administration and quality control of the treatment intervention and assessments
  - *Treatment compliance*
  - *Treatment integrity*
  - *Validity of baseline and outcome assessments*
  - *Contacting patients*

The measures used in the trial and their justification
- *Demographic information*
- *History of depression and treatment*
- *Current depression and service usage*
- *Description of the cancer*
- *Psychiatric diagnostic interview*
- *Depression*
- *Anxiety*
- *Physical functioning*
- *Confidence, problem-solving, social support*
- *Satisfaction*

Ethical approval

List of Tables

Table 4.1: Variables measured in the trial

DESIGN

The design was a single-centre randomised two-arm trial with a six-month follow-up and was based in the Edinburgh Cancer Centre. One arm was the experimental intervention arm and the other the 'control' arm which was essentially usual care. 'Usual care' was examined with respect to its ethical considerations and its content. A review of the evidence for the efficacy of current treatment was undertaken as discussed in the introduction to this thesis and the conclusion drawn that the current 'standard' treatment was evidence-based. In terms of content, during the pilot phase of this research I collected and analysed data to assess the 'standard' treatment received by 150 patients attending the Edinburgh Cancer Centre (Sharpe et al 2004a). Standard treatment consisted predominantly of GP care and antidepressant medication.

THE PATIENT SAMPLE

Population, number and source of subjects

Patients with both cancer and MDD were identified from an existing clinical screening programme in selected outpatient oncology clinics. Patients with lung cancer were excluded from large-scale screening as, in the majority of cases, their prognosis was poor and therefore completion of a six month trial was unrealistic and in terms of data completeness, the risk of loss of outcome data due to death would be high. However, referrals for diagnostic assessment and subsequent trial eligibility assessment were accepted and a small lung cancer clinic was screened later in the

trial. From a clinical perspective, there were some patient groups, such as 'head and neck' cancers and 'upper gastro-intestinal' cancers whose cancer may be related to alcohol use. Of this group, those patients identified with depression were likely to have considerable social problems and therefore a brief intervention administered by a non-mental health clinician was not considered to be appropriate and unlikely to be effective. Furthermore, from a practical perspective, patients with head and neck cancers may have residual communication problems making the talking therapy component of the intervention difficult for both the patient and the therapist. Those patients diagnosed with MDD and interested in taking part in the trial were assessed in a three-stage interview for trial eligibility.

Inclusion criteria

The principal inclusion criteria were that the patients had a diagnosis of cancer and were found on screening to have definite or probable MDD of at least a month's duration and have a SCL-20 score of at least 1.72. This score has been shown to have the highest positive predictive value amongst self-report measures for MDD (Mulrow et al 1995).

Exclusion criteria

Patients excluded from the trial were those with a survival of less than six months as predicted by their cancer specialist; with another complicating and uncontrolled medical problem (such as poorly controlled epilepsy or cerebral metastases) or where antidepressants were contraindicated for medical reasons; who were too ill to participate in treatment because of ongoing cancer therapy; who had a complicating

major psychiatric diagnosis (such as bipolar affective disorder, psychosis, severe known personality disorder) or an alcohol or substance misuse problem; who had chronic depression with a history of continuous depression for more than two years prior to the screening diagnostic interview; who were receiving active treatment for their depression from a psychologist or psychiatrist; who were judged to be in need of urgent psychiatric treatment; who were unable to communicate adequately because of language problems or cognitive impairment and who lived outside reasonable travelling distance.

Previous research in the Edinburgh Cancer Centre identified MDD in approximately 8% of patients attending selected oncology outpatient clinics (Sharpe et al 2004a). This research also showed that recruitment of eligible patients for the trial was sustainable from the clinics screened at a rate of four patients per week of which approximately 50% would refuse to take part in the trial. Based on these calculations over forty-five weeks of screening per year, to recruit two hundred patients (sample size discussed in next chapter) to the trial would take approximately two years. However, accepting referrals would reduce the estimated time required to recruit the necessary sample size.

THE PROCEDURE

Depression Screening

Patients with MDD were identified from consecutive cancer centre attenders (excluding those attending for initial cancer assessment) using a two-stage screening system. In stage one all patients completed the HADS questionnaire (Zigmond & Snaith 1983) on a touch screen computer or paper prior to their consultation with the oncologist at the following outpatient cancer clinics: colorectal, breast, gynaecological, genitor-urinary, sarcoma, melanoma, haematological, lung and mixed cancers. A threshold score (total HADS score $\geq$ 15) identified those patients likely to have MDD. I also used a threshold score on the HADS depression subscale of $\geq$ 10 to identify patients warranting further assessment. In stage two those patients whom the oncologist predicted had a survival of more than six months and who had scored high on the HADS (HADS$\geq$ 15 or HADS-D$\geq$ 10) or who on the automated screening had endorsed the question about suicidal ideation on the nine-item Patient Health Questionnaire (PHQ-9), (Kroenke et al 2001, Kroenke and Spitzer 2002), were interviewed after the consultation and at home over the telephone, using the SCID, in order to identify those with a diagnosis of definite or probable MDD. The telephone SCID interview has been shown to have high reliability with the in-person SCID, (Cacciola et al 1999, Simon et al 1993). Patients *referred* to the trial were screened using a one-stage procedure of the telephone diagnostic interview only.

All patients identified with MDD were assessed briefly for trial eligibility at the end of the diagnostic interview (stage 1), specifically for chronic depression and whether

they were already receiving treatment for their depression from a mental health specialist. Those patients who were not excluded at this stage were asked permission for their contact details to be passed to the research team and for information about the trial to be sent to them.

Baseline research assessment

I contacted those potentially trial eligible patients more than twenty-four hours after receipt of the trial information, thus allowing them time to consider participation as required by the ethics committee. Trial eligibility was assessed over the phone (stage 2) and for those patients potentially trial eligible, an interview time was arranged for a face-to-face interview (stage 3). At this interview the trial was explained and the patient completed the self-report Symptom Check-list, (SCL-20) (Derogatis et al 1974), to check eligibility on depression severity. Those scoring ≥1.72, the severity score set for this trial, were informed of the randomisation process and those who agreed to participate were consented for trial participation. At all stages, reasons for non-inclusion and refusals were recorded.

The Trial

At the eligibility interview, before consent was obtained and the patient formally entered into the trial, I answered all questions that the patient had, checked that the patient had understood what the treatments were, what randomisation meant, and that they would be willing to accept whichever allocated treatment they were offered. Written consent was then obtained, randomisation performed as described below and

the patient assigned a trial number. For patients excluded at any stage, I informed their GP and Oncologist of the patient's MDD diagnosis.

Randomisation

Justification for randomisation by minimisation

Allocation to treatment was concealed during randomisation. Randomisation was required in order to achieve comparable groups of known and unknown confounders. However, there is a risk in smaller trials that imbalances in baseline characteristics may occur. As this trial was relatively small and that there were certain 'suspected' patient characteristics or potential prognostic factors that should have been comparable at the beginning of the trial, some 'control' needed to exist to ensure that the allocation of patients to each group achieved a balance in certain baseline characteristics between the groups at the end of recruitment. For this reason I chose to restrict the randomisation using a method called minimisation. This method would not only ensure that the groups at the end of recruitment and allocation were comparable but also that each treatment allocation was unpredictable.

The randomisation procedure

To avoid individual trial team members knowing how the risk factors were accruing and therefore having the ability to predict and therefore influence allocation, the process of randomisation was handled by the Cancer Research UK clinical trials service independent of the trial team. This Unit supervised the registration of patients and operated the computerised randomisation by minimisation programme. This programme determined which group inclusion of a patient would minimise specific

differences in known or suspected determinants of outcome. In addition to this strategy, I chose to employ a random element in the allocation procedure of 0.75:0.25 to further decrease the probability of an individual predicting correctly the allocation. The value of the method of minimisation was shown by White and Freedman (1978) and Smith (1984).

The factors chosen for minimisation in this trial were: gender, age (≤ 39, 40-79, ≥ 80) disease site (colorectal, breast, gynaecological and 'other') and extent of disease (disease free, local disease, and metastatic disease).

Justification for minimisation factors

It was suspected that gender may be a determinant of outcome. The pilot study of this trial included very few men and it was therefore not possible to show any statistically significant differences between men and women in their response to treatment. From clinical experience however, men appear to be less likely to declare symptoms and are generally less willing to talk about their emotional well-being.

Another factor important when considering balanced and comparable groups was age as age was considered a possible prognostic factor in recovery from depression.

Disease site and extent of disease may have an effect on recovery but may also be of prognostic importance. From clinical experience, patients' reaction to recurrence of their cancer is often worse than initial diagnosis and therefore it seemed important to ensure comparable groups with regard to both disease and extent of disease.

Trial outcome assessments

Two research assistants conducted the outcome measures at three and six months and were kept blind to the patient's treatment status as far as possible. Both were trained in the administration of the SCID and all of the outcome SCID interviews were re-rated by another member of the research group trained in SCID interviewing, independent of the trial team and blind to the patient's treatment allocation. To minimise bias all the re-rated interviews were used in the final analysis.

The treatment evaluated in the trial

The two treatment conditions compared in the trial were optimised usual care and optimised usual care plus an experimental intervention.

Optimised usual care:

Usual care was what is currently practised. This was optimised by informing the patient's GP and Oncologist that their patient had MDD and providing management advice on request. It was anticipated that a minority of patients would be referred to specialist services.

Optimised usual care plus an experimental intervention:

A nurse-delivered intervention supplemented the optimised usual care. The intervention was based on the management of depression in primary care patients developed by the Seattle group (Katon et al 1995). It was delivered over a maximum of 10 sessions according to a detailed manual (see Appendix A), which included a treatment response algorithm to determine the number of sessions required. It had two phases:

1. The Treatment Phase: This was a nurse-delivered, psychiatrist-supervised treatment, comprising PST, enhancing social support and encouraging the use of antidepressant drugs. PST is a simple but flexible brief psychotherapy of proven effectiveness for MDD in non-cancer patients that can be applied to a wide variety of patient concerns (Hawton and Kirk 1989). PST was applied to problems chosen by the patient and nurse together and included addressing the patient's depression as a problem. The patient was also encouraged to see their GP to discuss taking an antidepressant drug and, if required, the nurse facilitated the prescription of antidepressants through direct contact with primary care. The patient was also encouraged to seek and use social support (both professional and personal), available to them. In the final sessions, the patient completed a 'relapse prevention plan' which is a self-monitoring schedule and action plan for the patient should they become aware of depressive symptoms returning. The patient's response to treatment was monitored during the intervention by the treating nurse using a depression severity measure. For this I selected the PHQ-9, which was routinely completed by the patient at the beginning of each treatment session.

2. The Monitoring Phase: Active monitoring of depressive symptoms using the PHQ-9 was performed monthly during the post-acute monitoring phase. Additional booster sessions up to a maximum of three, delivered by phone or face-to-face, were offered if relapse was identified or if the patient requested it.

Treatment was delivered in the Western General Hospital at the University of Edinburgh Cancer Research Centre. For those patients who during treatment were

unable to attend for individual appointments, telephone based or home based treatment sessions were conducted.

Recorded for individual patients for analysis were: number of sessions; completion of homework; total treatment time; total administration time; total supervision time from supervising clinician(s); total direct consultation time from supervising clinician(s) and details of antidepressant therapy including type, date commenced and dose increases.

Depression severity measure

The PHQ-9 depression severity measure is a brief self-report questionnaire (see Appendix B), which makes it useful clinically to determine treatment response. Its brevity allows quick completion and its self-report attribute eliminates observer bias, making it useful as a research tool. The PHQ-9 is the depression module of the full self-report PHQ (Spitzer et al 1999) derived from the PRIME-MD diagnostic instrument for common mental disorders (Spitzer et al 1994). It scores each of the nine DSM-IV criteria as 0 (not at all) to 3 (nearly every day). In terms of classifying severity, the PHQ-9 scores of 5, 10, 15 and 20 represent mild, moderate, moderately severe, and severe depression, respectively. However, the intention of using the PHQ-9 was as a measure of severity only. In a study of its criterion validity, measured against a structured mental health professional interview (based on the SCID and diagnostic questions from the PRIME-MD) by Kroenke et al (2001), it was shown to have a sensitivity of 88% and a specificity of 88% for MDD at a cut-off score of ≥ 10. It has been suggested that the PHQ-9 is sensitive to change over

time. From personal discussion with Professor Kurt Kroenke, I chose to operationalise a 'clinical treatment response' as ≥ 50% reduction in the PHQ-9 score from the pre-treatment score.

Modification of the trial treatment

A treatment guideline algorithm (in the Quality Control Manual Appendix C) was used to modify individual treatment programmes, which includes a formal assessment of clinical treatment response at session five. The treatment team reviewed all patients not achieving a treatment response in clinical supervision sessions. Review included: re-assessment; changes to the coping skills training or changes in the patient's antidepressant medication or dose. In addition, at any stage of the treatment programme, patients assessed as being at immediate high risk of suicide received an emergency review by the supervising psychiatrist or by a member of the hospital psychiatric team.

If the patient achieved a 'treatment response' during intervention, an individualised 'relapse prevention plan' was developed with the patient as per treatment manual (Appendix A).

Administration and quality control of the treatment intervention and assessments

The supervising consultant psychiatrist and I provided supervision for all the team members. The focus of the supervision for the treating nurses was adherence to the treatment model and discussion of problems arising during treatment. The focus of

supervision for the research assistants was adherence to the diagnostic criteria of the SCID assessment and discussion of cases difficult to diagnose for which a consensus decision on diagnosis was made.

Treatment compliance

Compliance of patients to the trial intervention was analysed according to the following definitions that were developed to incorporate the two components of the intervention that could be most accurately measured, antidepressant use and attendance for the face-to-face problem-solving treatment sessions with the nurse. Non-compliance was defined as not taking any antidepressant drugs and attendance for less than two sessions of problem-solving treatment; partial compliance was minimum compliance in either problem-solving (attendance for two sessions) *and/or* in antidepressant medication (taking an antidepressant drug); full compliance was attendance for more than two sessions (with completion of session work and homework) *and* taking an antidepressant drug at therapeutic dose of antidepressant as doses greater than the minimally effective doses according to prescribing guidelines (Taylor et al 2005) , modified to accept 75mg as effective for tricyclic antidepressants (Furukawa et al 2002).

Treatment integrity

All therapists were registered nurses with experience in oncology trained according to a manualised protocol (in Appendix C). Training was delivered over six months on a part-time basis (twenty-five hours per week) and all therapists were certified for competency prior to starting treatment in the trial. Certification entailed completion

and assessment of training in communication skills, SCID diagnostic assessment, suicide risk assessment and management, basic antidepressant medication knowledge, case-management, self-management, treatment adherence monitoring, and problem-solving therapy. Assessment of the major components of the training was conducted using review of role-play sessions plus assessment of the treatment delivered to at least five patients and adherence to the treatment manual formally assessed on the last two patients treated.

Therapists received weekly supervision from the supervising psychiatrist. All therapy sessions were video-taped and treatment integrity assessed at three monthly intervals on a randomly selected sample of at least five sessions. Treatment integrity was defined as adherence to the treatment protocol in at least 80% of the sessions reviewed over the twenty-four months of treatment delivery and assessed according to the Quality Control Manual (Appendix C). In addition to this, should a therapist fail an adherence assessment, thereafter a 5% randomly selected sample of all session recordings would be assessed for treatment integrity by an independent assessor.

Validity of baseline and outcome assessments

In order to make the diagnostic SCID assessment as valid as possible, a second rater, blind to the patient's allocated treatment and independent of the trial team, reviewed taped recordings of the SCID assessment, edited to remove any reference to treatment, and re-rated the assessments. All the re-rated interviews were used in the final analysis.

Contacting patients

Before conducting any trial follow-up assessments, the patient's survival status was checked by contacting the patient's GP practice. For non-responders to phone and/or questionnaire follow-up, a reminder letter was sent to the patient. If still no questionnaire data was received, the team attempted to contact the patient again to obtain the minimal data (SCL-20) by telephone interview. If all data was refused a reason was obtained and recorded.

THE MEASURES USED IN THE TRIAL AND THEIR JUSTIFICATION

I chose to use both self-rated scales and interview-based measures to increase the robustness of the findings. At baseline, three months and six months, all patients in the trial were asked to complete self-report questionnaires (appendix D) and a diagnostic assessment and semi-structured interview over the telephone as listed in Table 4.1.

From pilot data, the time point at which the maximum effect of treatment was detectable was at three months and I therefore chose this as the principal outcome time point. Three months after entry to the trial, there is also less likelihood of missing data due to patients dying or becoming too ill to participate. However, measures were also planned at six months to look for persistent and stable improvement.

The principle outcome measure for the trial was the difference in mean scores on the SCL-20 measure between the treatment groups at three months.

The secondary outcome measures were to compare between treatment groups at three months: a) the proportions with a treatment response dichotomised on the SCL-20 as those patients achieving or not achieving a 50% reduction in the total SCL-20 score from their baseline score (baseline scores had to be ≥ 1.72); b) the proportions of patients no longer meeting DSMIV criteria for MDD; and c) the proportions achieving remission of depression as defined by a SCL-20 score of <0.75.

The measures used are summarised in table 4.1 and described in more detail in the section that follows.

Table 4.1 Variables measured in the trial

Semi-structured interview
Demographic information
History of depression and treatment
Current depression and service usage
Cancer status (and from medical notes)
Psychiatric diagnostic interview (by telephone)
Psychiatric diagnosis of MDD
Self-rating scales (by mailed questionnaire)
Symptoms of depression
Symptoms of anxiety
Physical functioning
Subjective rating of confidence, problem-solving ability, and social support
In addition, at 6 months only:
Satisfaction with depression care

Demographic information

Data was collected at the eligibility assessment interview on the following: age, gender, marital status, whether living alone and employment status. The Scottish Index of Multiple Deprivation (SIMD) score (Scottish Executive 2004) was calculated from the patient's postal code. This score defines poverty in terms of

relative deprivation by combining information from all five deprivation domains: income, employment, health, education and access to services. A higher score represents more poverty.

History of depression and treatment

Data about previous episodes of depression, about treatment received and duration of treatment was collected at the eligibility assessment interview. In addition to this, any psychiatric notes were reviewed.

Current depression and service usage

At the diagnostic telephone interview, current depressive symptomatology was assessed and date of onset of the current depressive episode noted. Current usage of antidepressant medication, psychological services, complementary and alternative therapies and of health services was also recorded. For the three and six month assessment interviews, the recording of service usage related to the previous three months.

Description of the cancer

I reviewed the patient's oncology case notes prior to randomisation to extract data on the following: disease site and diagnosis; first or second diagnosis; primary or recurrent; extent of disease (disease free, local disease, metastases); current management (monitoring, under investigation, pre-treatment); and whether on active treatment (radiotherapy or chemotherapy), using a data collection form and working data definitions validated by an oncologist (see appendix E).

Psychiatric diagnostic interview

The presence of MDD and depressive symptoms was determined at the diagnostic assessment interview using the MDD section of the SCID. MDD requires the patient to have experienced at least five of nine specified symptoms during the same two-week period in the previous month and must represent a change from previous functioning. One of the five symptoms must either be persistent depressed mood or loss of interest or pleasure in all or almost all activities. Other symptoms included in the diagnostic criteria are: insomnia or hypersomnia; significant increase or decrease in weight or appetite; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or inappropriate guilt; diminished ability to think or concentrate or indecisiveness; recurrent thoughts of death or suicidal ideation.

Complexity arises in assessing depressive symptoms of patients with medical illness as many of the symptoms of medical illness are similar to symptoms of depression. Of the advocated solutions to this, there are two approaches appropriate for the cancer population. The first is the 'exclusive' approach which originated from research done by the Sloan-Kettering Cancer Institute, (Bukberg et al 1984; Plumb and Holland 1981) that advocates eliminating the symptoms of anorexia and fatigue from the nine symptoms of the SCID and making the diagnosis of MDD reliant on meeting four out of the remaining seven symptoms. This approach makes it harder for patients to meet the restricted criteria and may result in a loss of sensitivity, leading to false negatives. The alternative approach for cancer patients is the reverse of the 'exclusive' approach. The 'inclusive' approach used by Rifkin and colleagues (1985), whereby diagnostic decisions are made on the evaluation of observable

phenomena, does not require aetiologic inferences as advocated by Spitzer and colleagues (1984), the developers of DSM-III. Its sensitivity may therefore be high but specificity lower, possibly leading to over-diagnosis of MDD. I have chosen the latter approach for the following reasons. From clinical experience, fatigue and anorexia are not the only two symptoms shared by patients with the illnesses, cancer and depression. Depending on the nature of the anticancer treatment, and the extent of disease, other physical and psychological criteria of the MDD diagnosis can also be present in patients with cancer, such as insomnia and diminished ability to think or concentrate. This, together with the need for a method of assessment that requires as little subjective assessment as possible to increase inter-rater reliability, has influenced my choice of the 'inclusive' approach for this research trial.

Symptoms were therefore counted toward the diagnosis if present and no judgements about the aetiology of particular symptoms were made. The interview is a semi-structured interview and requires training of those individuals administering the interview. All researchers involved in this trial were trained in its use and deemed competent in formal assessment including review of taped interviews. Its use by trained clinicians offers a reliable diagnosis (Williams et al 1992) and is considered the 'gold standard' interview. For this trial the interview was administered by telephone. Telephone administration of the SCID interview has been previously shown to be acceptable to patients (Allen et al 2003).

Depression

I chose the 20 –item Hopkin's Symptom checklist Depression Scale (SCL-20) as the principle outcome measure with the primary outcome being the difference in mean scores on the SCL-20 measure between the treatment groups. The SCL-20 has been used as an outcome measure in primary care clinical trials of depression management (Katon et al 1995; Katon et al 1996; Williams et al 2000). It has been found to have high reliability and validity in multiple studies with medical patients and to be sensitive to change in depressed primary care patients (Derogatis et al 1974). It is a short self-report measure derived from the SCL-90 (Derogatis et al 1973) asking the patient to rate the presence of symptoms 'in the past month', on a measure of a severity scoring system in the following categories: 'not at all'; 'a little bit'; 'moderately'; 'quite a bit'; and 'extremely', scoring 0-4. The score is calculated by dividing the sum of the scores of each question by the number of questions.

Current criteria for determining improvement in depression aim to distinguish between different degrees of symptomatic improvement, such as remission or response. Remission is considered to be a marker of wellness for various chronic medical illnesses and treatment is often given until remission is achieved. Similarly remission of symptoms serves as a marker of wellness in mood disorders and can serve as a clinically relevant marker for optimal treatment outcome (Keller 2003). Based on this concept and on treatment outcome definitions used in similar clinical trials, I chose to distinguish between a treatment response (50% reduction in the SCL-20 score from baseline) and remission (a SCL-20 score of <0.75). Remission was defined in trials of primary care patients by Katon's research group as <0.5

(Unutzer et al 2002). However, remission of depression may be harder to achieve in cancer patients because of the high somatic symptoms associated with the disease. This is further complicated by the fact that cancer patients are often older and consequently more likely to have other medical problems. Therefore after discussion with Professor Wayne Katon, a remission score for the group of patients chosen for this trial of <0.75 was thought to be more clinically realistic. This score was arrived at by taking the minimal plausible score for patients without depressive symptoms together with the maximum scores for somatic symptom items to reflect high cancer symptom burden.

Anxiety

Anxiety was measured using the 10 anxiety items of the SCL-90 questionnaire (Derogatis et al 1973). The questions relate to symptoms or feelings experienced "over the last week, including today", on a severity scoring system in the following categories: 'not at all'; 'a little bit'; 'moderately'; 'quite a bit'; and 'extremely', scoring 0-4 respectively. The final score is the average of the item scores.

Physical functioning

Physical functioning was assessed using the physical functioning scale from the EORTC-QLQ-C30 (Aaronson et al 1993) self-report measure. The EORTC-QLQ-C30 is a widely used self-report measure in clinical trials shown to have good reliability and validity. The physical functioning scale has 5 items and a total score of 0-100, higher scores representing better functioning (Fayers et al 2001).

Confidence, problem solving ability, social support

Identifying the mechanism of action of problem-solving therapy would logically direct research to measurement of self-efficacy, such as confidence, and control. However a recent trial of depressed patients in primary care suggests that self-control, mastery, and perception of problem severity may be proxy measures of depressed mood (Mynors-Wallis 2002). Depression therefore appears to confound the determination of the mechanisms of action of problem-solving therapy. I have adapted available measures to focus mainly on measures of problem-solving ability using the 'problem-solving and coping strategies' items from the IMPACT study measures and have included one simple question to measure self-efficacy also used in the IMPACT study (Unutzer et al 2002). Self-efficacy (confidence) was measured using a simple Likert-type scale ranging from 0-10. Problem-solving ability was assessed using three items concerning ability to address problems and the ability to consider the pros and cons of possible solutions, each item being scored individually on a scale of 1-4. For all scales higher scores indicated better coping.

In terms of measures of social support, there is a lack of consensus on the definition of social support. The variability occurs around the concept, mainly: type of support; perceived availability versus actual support received; and amount of support versus actual, (Shroevers et al 2003). Furthermore, the reliability and validity of most social support scales have not been adequately tested. Having reviewed many measures, I have adapted measures used in the IMPACT study (Unutzer et al 2002), resulting in two simple questions concerning perceived availability of support and likeliness to use the support available which performed as a scale, ranging from 2-8.

Satisfaction

At six months, in addition to the above measures, satisfaction with depression care was assessed using a 7-point scale as used in similar trials (Unutzer et al 2002), a score of 1 representing 'no care received', 2 'can't answer' and 3-7 poor to excellent, 3 being 'poor' and 7 being 'excellent'.

ETHICAL APPROVAL

The patient's consent to participate in the trial was obtained after a full explanation had been given of the treatment options, including the conventional and generally accepted methods of treatment. The patient information sheet and patient consent form are attached (see Appendix F). The right of the patient to refuse to participate in the trial without giving reasons was respected. Similarly, the patient was free to withdraw at any time from the protocol treatment or from the trial without giving reasons and without prejudicing his/her further treatment.

For all patients their GP was informed of their progress following each trial assessment. Management advice was given or direct referral to the hospital psychology services was made.

The protocol for this trial was approved by the Local Research Ethics Committee (LREC), division of Primary Care/Public & Mental Health Research, LREC Number 2002/7/39. LUHT NHS R&D approval was also obtained – approval reference number 1632.

CHAPTER 5: ANALYSIS OF DATA AND STATISTICAL POWER

Sections

Analysis of Data
- Data handling
- Representativeness of study sample and throughput
- Descriptive data
  - *Baseline characteristics*
  - *Baseline measures*
- The treatments
  - *Nurse therapist efficacy*
  - *Treatment integrity*
  - *Treatment compliance*
  - *Non-trial treatments received during the trial*
- Missing data
- The trial
- Primary outcome
  - *Sensitivity analysis*
  - *Subgroup analysis*
- Secondary outcomes
  - *Depression measure*
  - *Relative measures of effect*
  - *Anxiety, physical functioning and coping measures*
- Six month follow up
  - *Secondary outcomes*
  - *Satisfaction with care*
- Exploratory analysis
  - *Process of change*
  - *Exploration of baseline predictors of outcome at three months*
- EORTC-QLQ-C30

Sample size and power calculation

ANALYSIS OF DATA

Data handling

Data from stage one of the screening process was imported from the touch screen computers in the outpatient department using Excel and downloaded into the individual patient file in the Trial's main Access Database. Data from the second stage of screening was entered manually from the paper scoring sheets completed during the telephone diagnostic interview and the relevant telephone recording (digitally taped using Retell software) attached to the patient's database file in WAV format. All other data was entered from the paper forms into the Access database. All hand entered data was checked for errors. In addition to this, data was checked for errors of entry by looking for extreme values. All possible errors were checked back against the paper forms.

All data were analysed using the statistical package SAS version 9.1 and STATA version 9. The analysis was then performed in a systematic fashion to test pre-stated hypotheses as follows.

Representativeness of study sample and throughput

Patient throughput from initial screening to trial recruitment was reported, detailing reasons for patient exclusion and trial refusal. Data for the whole group and those patients refusing trial participation were described with respect to age, gender, cancer type and social deprivation score.

The throughput of patients after randomisation to the trial through follow-up at three and six months was summarised using the system recommended in the CONSORT statement on the reporting of trials (Moher et al 2001).

Descriptive data

Data for the whole sample and by treatment group were described. Binary and categorical variables were presented using numbers with percentages, continuous using means and standard deviations, or in the case of non-normal data, medians and ranges. No tests of statistical significance were conducted for differences between the randomised groups for any baseline variable.

Baseline characteristics

The patients' baseline characteristics were described with respect to age, gender, marital status (married or cohabiting, single, divorced or separated and widowed), living situation (living alone, living with partner and other living arrangement), employment (professional, clerical, manual, unemployed, student, housewife/husband, medically retired and retired), social deprivation, depression variables (duration of current depressive episode, previous number of depressive episodes), current depression treatment (GP contact, antidepressant prescribing, medication adherence), cancer variables (cancer type, number of primary cancers, time since first diagnosis, time since most recent cancer diagnosis, extent of disease, treatment stage) and current cancer treatment (radiotherapy, chemotherapy or both).

Baseline measures

The patients' baseline measure scores were described with respect to initial screening HADS, depression (the number of SCID items endorsed and SCL-20 score), anxiety, physical functioning and coping. As the whole EORTC-QLQ-C30 was used for assessment, the global health and quality of life, and the functioning and symptom scales were also described at baseline.

The treatments

Nurse therapist efficacy

The relative efficacy of the nurse therapists was determined by comparing patient outcome between therapists. No statistical analysis was performed as allocation of patients to therapists could not be random for practical reasons.

Treatment integrity

Treatment integrity was presented as the percentage of face-to-face sessions rated as adhering to the treatment manual on a randomly selected sample of at least 10% and on a further 5% randomly selected sample by an independent assessor.

Treatment compliance

Treatment compliance of the patients in the intervention group was presented as the proportions of patients achieving full, partial or no compliance together with the number of therapy sessions attended shown for each category of compliance.

Non-trial treatments received during the trial

The use of services in the three months preceding the trial outcome assessments other than those delivered in the trial were described by treatment groups with respect to use of GP services, mental health specialists, clinical nurse specialists, counselling services and complementary/alternative therapies.

Missing data

Individual scales were examined to assess the level of missing responses. In accordance with the EORTC scoring manual, missing scores on the EORTC questionnaire were taken as the average of all present items when less than half the items on a scale were missing, but were considered missing when at least half of the items were missing. For the SCL-20 and SCL-90 measures, when less than half the items measure were missing, the scale score was calculated by dividing the total item scores by the number of questions answered.

The trial

The study was designed to determine whether supplementing optimised usual care with the nurse-delivered intervention achieved a greater improvement in depressive symptoms at three months after randomisation than optimised usual care alone.

An "intention to treat" analysis strategy was employed (Pocock 1983). This is used in analyses of RCTs and compares all patients in the groups to which they were originally randomly assigned, even if they did not complete treatment or were later found not to meet eligibility criteria. The use of this method of analysis reduces the

risk of overestimating the clinical effectiveness of a treatment (Hollis and Campbell 1999).

Primary outcome

The relative efficacy of the two treatment conditions was determined by calculating the statistical significance of the difference in mean scores on the self-report SCL-20 between the treatment groups at three months after randomisation. A P value of 0.05 was taken to indicate statistical significance. Analysis of Covariance (ANCOVA) was performed using the three month SCL-20 score as the dependent variable whilst adjusting for the baseline SCL-20 score and the minimisation variables of age, gender, diagnosis and extent of disease. The validity of this method of analysis was examined by confirming that the residuals from the fitted model were normal in distribution. The adjusted mean difference between the groups was presented in tabular format with 95% confidence intervals and corresponding P value and graphically as a dot plot indicating the change from baseline to three months in mean SCL-20 score $\pm$ 2 standard errors by treatment groups. The standardised effect size was calculated.

Sensitivity analysis

The analysis for the primary outcome was repeated imputing a 'no change score' for patients with missing data and presented in tabular format.

Subgroup analysis

An interaction term was fitted into the ANCOVA model for the three month SCL-20 to determine whether the treatment effect was different in the subgroups for age (age band <40, 40-79 and ≥80; cancer type (breast, colorectal, gynaecological and other cancers); disease extent (disease free, local disease and metastases) and gender. The results were presented with P values to indicate statistically significant interactions.

Secondary outcomes

All secondary analyses were performed for exploratory purposes only. Statistical significance was defined as a P value of 0.01 to limit chance findings as a result of multiple testing.

Depression measure

The relative efficacy of the two treatment conditions was further determined by comparing the proportions of patients achieving a clinically significant outcome between the treatment groups at 3 months. Clinical significance was specified as a 50% reduction in SCL-20 score from baseline; a SCL-20 score of <0.75 and no longer meeting the criteria for MDD on the SCID. All analyses were performed using logistic regression adjusting for baseline measurement and minimisation factors and the intervention effect was presented as Odds Ratio with 95% confidence intervals and P values.

Relative measures of effect

In order to examine further the clinical significance of the results several additional calculations were made. The relative risk reduction, absolute risk reduction and number needed to treat were presented for all clinical indicators and standardized effect size calculated for the interview-based outcome with 95% confidence intervals.

Anxiety, physical functioning and coping measures

Differences in the other secondary outcome measures, (EORTC-QLQ-C30 physical functioning scale, SCL-90 10 item anxiety measure and coping measures), between the treatment groups were also compared to illustrate and elaborate the main finding. Measures not normally distributed were transformed and ANCOVA was used for all measures other than problem-solving, adjusting for baseline SCL-20 scores, minimisation factors and the outcome measure. The mean difference was presented as the intervention effect with 95% confidence intervals and P values. For the problem-solving measure, each item was analysed separately as a comparison between the treatment groups from baseline to three months in the proportions endorsing values representing good problem-solving skills.

Six month follow up

Secondary outcomes

No statistical analysis was undertaken at six months as three months was the primary outcome. The six month outcome was described in two ways: first by describing, by treatment groups, the proportions with no change or improvement on all secondary

outcomes (50% reduction in SCL-20 score from baseline; a SCL-20 score of <0.75; no longer meeting the criteria for MDD on the SCID; EORTC-QLQ-C30 physical functioning scale; SCL-90 10 item anxiety measure; and coping measures) and second by plotting the raw SCL-20 scores by treatment group over time presented as a box plot.

Satisfaction with care

For a satisfaction rating of care received during the trial, the proportions endorsing care in seven categories of 'no care received' to 'excellent' was presented in a table.

Exploratory analysis

Process of change

Changes in measures of a) confidence, b) coping, and c) social support, were examined at three months as a measure of treatment process. To establish whether improvement in depression scores was mediated by improvement in aspects of confidence, coping and support, change in SCL-20 depression scores for each treatment group was plotted against changes in each of the coping items measured and its association examined using Spearman's Rank Correlations Coefficient with P values at the 1% level to indicate significance.

Exploration of baseline predictors of outcome at three months

To identify independent predictors of adjusted SCL-20 score (adjusted for treatment and baseline SCL-20 score) at three months, a model was fitted to include extent of disease, duration of depressive episode and number of previous episodes (as categories of duration more or less than 1 year, and no episodes versus any)

alongside treatment and SCL-20 baseline score and presented in tabular format to show effect estimates and p-values.

EORTC-QLQ-C30

All analyses were exploratory. Chance findings resulting from multiple testing could have occurred therefore even when significance was taken at the 1% level all results were considered as an area highlighted for future study rather than a statistical finding. The scales analysed were those examining functioning (role, emotional, social and cognitive), global health and quality of life, pain and fatigue.

Analysis of covariance was performed, adjusting three month scores for baseline score and the four minimisation factors (age, sex, diagnosis and extent of disease). The adjusted mean difference between the groups was presented in tabular format with 95% confidence intervals and corresponding p value.

SAMPLE SIZE AND POWER CALCULATION

The purpose of a sample size calculation is to ensure that the proposed study has a high chance of detecting, as statistically significant, a worthwhile or clinically significant effect if it exists, and also to enable us to be reasonably sure that no such benefit exists if it is not found in the trial.

We considered a difference in proportions of 20% as a clinically meaningful difference. The initial power calculation was therefore based on detecting a 20% difference in the proportion of responders (from 20% to 40% of patients achieving a treatment response defined as a 50% reduction in their SCL-20 score from baseline). This required 200 cases in total to achieve 80% power with a two-sided significance level of 0.05 and allowing for an attrition rate of 10%. When the analysis plan was written prior to trial closure, unblinding and analysis, it was decided to change the primary outcome to be a difference in the *mean* SCL-20 score on the advice of the senior statistician. The reason for this was to maximize the ability of this efficacy trial to detect a difference between the treatments. When other similar trials were examined to identify a difference in mean SCL-20 score that equated with our previous definition of a clinically meaningful treatment response of a 20% difference in the proportions of responders, a difference in means of 0.21 on the SCL-20 was identified. This was based on both personal communication with Professor Wayne Katon and from the results of the IMPACT trial (Unutzer et al 2002) of a difference in mean SCL-20 scores of 0.28 and standard deviation of 0.5 at four months between the control and intervention group. The sample size was therefore re-calculated using

the previous statistical assumptions of 80% power with a two-sided significance level of 0.05 and allowing for an attrition rate of 10%as follows:

Calculation formula from Altman 1991:

$$n = \frac{2\sigma^2 (U\alpha + U\beta)^2}{\theta^2}$$

where:

n = number of patients per group

σ = Standard deviation

θ = effect size (i.e. difference in proportions)

$U\alpha$ and $U\beta$ are values calculated from the normal distribution, depending on alpha and beta. For continuous data: at 80% power $U\alpha$ = 1.96 and with a standard deviation of 0.5 $U\beta$= 0.84.

therefore:

$$n = \frac{2 \times 0.25 \times (1.96 + 0.84)^2}{0.21^2}$$

n=88.89

Based on pilot work for this trial patient attrition would be less than ten percent.

Adjusting for 10% loss of follow-up data: $\frac{88.89}{0.9} = 98.77$ per group

Therefore with a total sample size of at least 198, 99 in each group, at a significance of 5% and a power of 80%, I would be able to detect a true difference of 0.21 in the mean SCL-20 scores between the groups, when it was used as a continuous scale assuming a standard deviation of 0.5.

RESULTS

Chapter 6: Trial Results

Chapter 7: Explorations of Predictors of Outcome

CHAPTER 6: RESULTS

Sections

Recruitment of the trial sample
- Depression screening
- Exclusions
  - *Medical exclusion*
  - *Psychiatric exclusion*
  - *Exclusion 'other reasons'*
  - *Failure to meet study criteria for MDD on the SCL-20 depression measure*
- Refusals
- Final sample size

Demographic characteristics of the sample at baseline
- Gender
- Living arrangements
- Deprivation
- Employment

Illness characteristics of the sample at baseline
- Depression
  - *Depression scores*
- Cancer
  - *Cancer type*
  - *Cancer characteristics*

Flow of patients through the trial

Demographic characteristics of the treatment groups at baseline

Illness characteristics of the treatment groups at baseline
- Depression
  - *Depression scores*
- Cancer
  - *Cancer type*
  - *Cancer characteristics*
- Subsidiary measures in the treatment groups at baseline

The treatments
- Administration and quality assurance of the treatment
  - *Treatment compliance*
  - *Treatment integrity*
- Untoward events during treatment
  - *Intervention group*
  - *Usual care group*

Experiences during treatment
Engagement
Behavioural activation
Antidepressant medication
Cognitive change
Support
Pre-illness personality and psychiatric morbidity
Non-attendance for therapy sessions
Other treatments received during the six months of the trial

Missing data

Outcome at three months
Outcome response
Primary trial outcome
Robustness of outcome to missing data
Standardised effect size
Relative risk reduction
Absolute risk reduction
Number needed to treat
Other secondary trial outcomes

Outcome at six month follow up
Secondary outcomes
Depression
Anxiety, physical functioning and coping
Satisfaction

Treatments received during the trial

Comment

List of Tables

Table 6.1: Reasons for refusal at each stage of screening and assessment

Table 6.12: Reasons for exclusion at each stage of screening and assessment

Table 6.13: Reasons for ineligibility at each stage of eligibility assessment

Table 6.14: Reasons for trial refusal at each stage of assessment

Table 6.15: Demographic characteristics of trial participants versus refusers

Table 6.16: Demographic characteristics of the sample

Table 6.17: Deprivation and employment characteristics of the sample

Table 6.18: Baseline depression characteristics of the sample

Table 6.19: Baseline depression scores of the sample
Table 6.2: Baseline cancer characteristics of the sample
Table 6.21: Demographic characteristics of the treatment groups at baseline
Table 6.22: Deprivation and employment characteristics of the treatment groups at baseline
Table 6.23: Depression characteristics of the treatment groups at baseline
Table 6.24: Depression scores of the treatment groups at baseline
Table 6.25: Cancer types of the treatment groups at baseline
Table 6.26: Cancer characteristics of the treatment groups at baseline
Table 6.27: Subsidiary variables in each treatment group at baseline
Table 6.28: Depression scores of the intervention group at the 3 month follow up by therapist
Table 6.29: Use of health services during the trial
Table 6.3: Time of trial outcome assessments
Table 6.31: Pre-specified primary outcome: comparison of adjusted SCL-20 score at 3 months by treatment group
Table 6.32: Pre-specified primary outcome: sensitivity analysis of comparison of adjusted SCL-20 score at 3 months by treatment group
Table 6.33: Subgroup analysis for interaction effect
Table 6.34: Pre-specified secondary depression outcomes: comparison at 3 months of treatment response and remission by treatment group
Table 6.35: Remission with core depressive symptoms at 3 months by treatment group
Table 6.36: Treatment effects for clinically relevant outcomes at 3 months
Table 6.37: Secondary outcomes: comparison at 3 months of physical functioning, anxiety and coping by treatment group
Table 6.38: Secondary outcomes: comparison from baseline to 3 months of problem solving by treatment group
Table 6.39: Depression outcomes at 6 months by treatment group
Table 6.4: Secondary outcomes at 6 months by treatment group
Table 6.41: Satisfaction ratings at 6 months by treatment group

List of Figures

Figure 6.1: Flowchart of screening and assessment of patients for probable or definite MDD

Figure 6.2: Flowchart of screening and assessment for trial recruitment

Figure 6.3: Pie chart of cancer type of the sample

Figure 6.4: Consort diagram of flow of patients through the trial and follow up

Figure 6.5: Histogram of studentised residuals from ANCOVA model

Figure 6.6: Dot plot of change in SCL-20 score over first 3 months by treatment group

Figure 6.7: Bar chart of remission on SCID at 3 months by treatment group

Figure 6.8: Box plots of SCL-20 scores at 3 and 6 months by treatment group

Hypothesis: *Usual care plus a nurse-delivered, psychiatrist-supervised multi-component treatment intervention reduces symptoms of major depressive disorder in patients with cancer to a greater extent than usual care alone.*

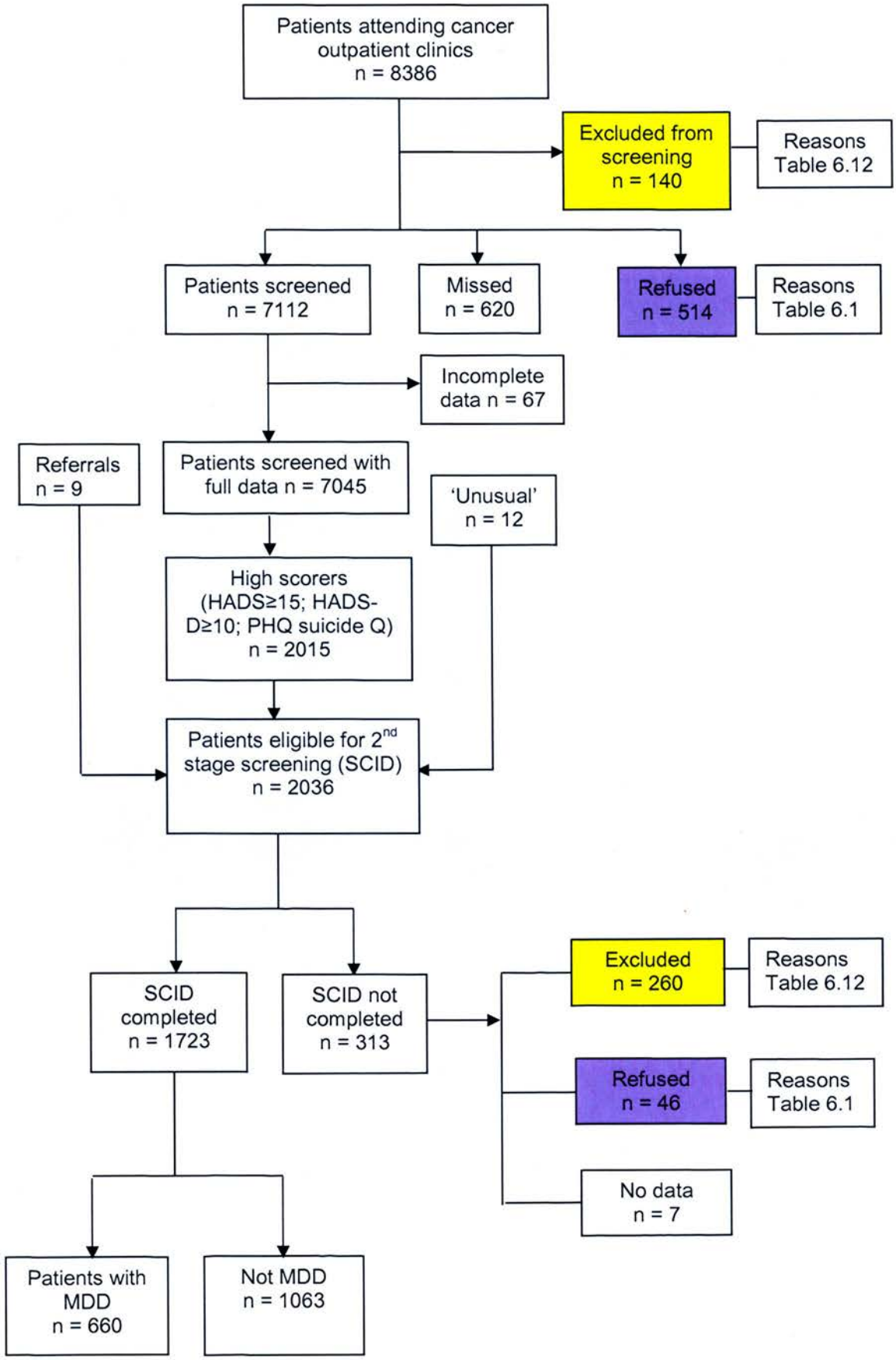
RECRUITMENT OF THE TRIAL SAMPLE

Depression Screening

Between 20th June 2003 and 13th January 2006, 8,386 patients were screened using the HADS and the PHQ as part of an automated touch screen symptom screening system and for a smaller proportion only the HADS as a paper version. The automated system is a symptom screening service developed by our Research Group. As routine practice all patients attending the Edinburgh Cancer Centre outpatient department are invited to complete symptom screening questionnaires prior to their oncology consultation. Those patients attending cancer clinics held elsewhere in the Hospital completed a paper HADS only. Patients who had scored a total HADS score ≥15 or a score of ≥10 on the depression subscale or who had endorsed a question about suicidal ideation on the automated PHQ were identified for further assessment. Referrals of patients from Consultants were also accepted for further assessment. Further assessment involved a phone delivered SCID to identify those patients with probable or definite Major Depressive Disorder.

Because patients were screened at every clinic attendance, each patient had multiple screening events recorded. In order to report on patients as opposed to their multiple screening events, the data for this dataset was selected on the patient's last positive (MDD) SCID. For those who did not receive a SCID their last high scoring screening event was selected. For those who did not score high on stage 1 screening (questionnaire), their last screening event within the time frame was selected. The details of this are illustrated in Figure 6.1.

Figure 6.1 Screening and assessment of patients for probable or definite MDD.



Over 30 months of screening, 8,386 patients were screened in the following outpatient cancer clinics: colorectal, breast, gynaecological, genitourinary, sarcoma, melanoma, haematological, lung and mixed cancers. Referrals from Oncologists were also screened for depression (n=9). Of the 8,386 patients, 560 (7%) refused screening (stage1 and stage 2 combined), with most refusing to stage 1 screening (514 refused stage 1 questionnaire screening and 46 refused the stage 2 SCID interview [see table 6.1]). Of the 8,386 patients, 400 (5%) patients were excluded from screening (140 excluded at stage 1 screening and 260 excluded from stage 2 SCID [see table 6.12]). We missed screening 620 (7%) patients and incomplete or no data accounted for 74 patients. We therefore screened 6732 (80%) of the patients attending the outpatient cancer clinics during the stated time period.

Table 6.1 Reasons for refusal at each stage of screening and assessment (reasons are exclusive) (n=560)

Refusal reason	**At clinic screening n=514**	**At SCID interview n=46**
Doesn't want to do it/ Doesn't feel it would help	403	18
Questionnaire/assessment issues	43	3
Doesn't feel depressed/anxious	20	0
Receiving care already/Prefers to see other health care professional	17	3
Feels emotionally too unwell	12	3
Last clinic visit/ Nothing has changed since last visit	11	n/a
Too busy/too many problems/ Wants to work on it themselves	3	5
*Other**	2	1
No data	3	13

*Recently bereaved (1); worried about confidentiality (2)

Table 6.12 Reasons for exclusion at each stage of screening and assessment (reasons are exclusive) (n=400)

Exclusion variable	At clinic screening n=140	At SCID interview n=260
Unable to contact	n/a	98
Advised by Oncology staff not to screen/assess	4	77
Too unwell	56	21
Communication problems	29	14
Interrupted screening/protocol change/screened recently (< 6 weeks ago)	32	10
Cognitive problems	15	4
Deceased	n/a	10
*Other**	4	15
No data	0	11

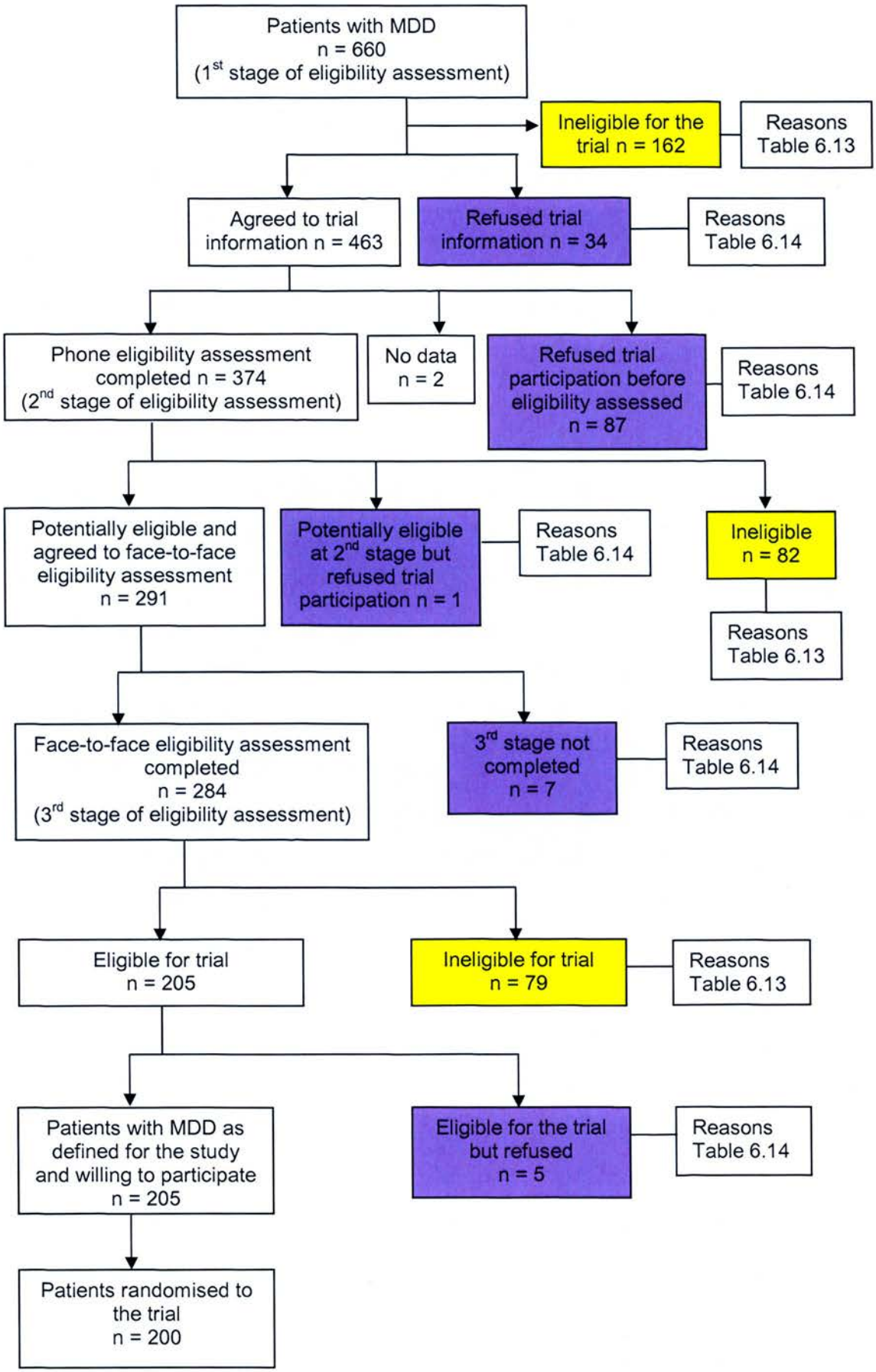
*Borderline HADS (7); assessment not done as prior to start of trial (5); patient already being used as 'training patient' (2); handcuffed (2); receiving care already (1); questionnaire completed by escort nurse (1); attending cancer centre for 2nd opinion only (1).

Of the 7,045 patients who completed stage 1 screening in clinic, 2015 (29%) patients scored high on the HADS (HADS $\geq$ 15 or HADS-D $\geq$ 10) or had endorsed the question about suicidal ideation on the PHQ-9 questionnaire. 2036 patients proceeded to stage 2 of the screening, which included 9 referrals from clinicians and 12 patients who had appeared low in mood in clinic, had declined stage 1 screening but had agreed to the telephone interview. Of the 1723 completed SCID interviews, 660/1723 (38%) patients were diagnosed with MDD on the SCID. The MDD prevalence rate (unadjusted for the 20% not screened) in patients attending (selected) outpatient cancer clinics at the Western General Hospital is 7.9% (660/8386).

From the patients screened (as described above), 660 patients were diagnosed with MDD from the telephone SCID interview. The flow of patients through the screening

and assessment stages of trial recruitment is shown in Figure 6.2. All patients diagnosed with MDD with an expected survival status of more than 6 months as indicated by their hospital consultant, were approached about the trial.

Figure 6.2 Screening and assessment for trial recruitment.



Exclusions

Trial eligibility was assessed in 3 stages: A brief assessment obtained during the SCID interview, designed to exclude the majority of people with chronic depression or high suicide risk; a semi-structured telephone assessment designed to identify those patients for whom travel would be burdensome thus avoiding patients having to travel unnecessarily to the hospital for assessment; and a semi-structured face-to-face assessment interview, designed primarily to exclude those patients with lower severity depressive symptoms.

The results of the 3-stage trial eligibility assessment are discussed below and detailed in Table 6.13. Reasons for ineligibility are not exclusive. Clustering of multiple reasons for trial exclusion occurred most frequently in reasons for psychiatric exclusion.

Exclusion criteria

Patients excluded from the trial are those:

a. with an expected survival of less than 6 months as predicted by their cancer specialist
b. with another complicating and uncontrolled medical problem (such as poorly controlled epilepsy or cerebral metastases) or where antidepressants are contraindicated for medical reasons
c. who are too ill to participate in treatment because of the cancer or its treatment
d. who have a complicating major psychiatric diagnosis (i.e. bipolar affective disorder, psychosis, severe personality disorder) or an alcohol or substance misuse problem
e. who have chronic depression with a history of continuous depression for more than two years prior to the screening diagnostic interview
f. who are receiving active treatment for their depression from a psychologist or psychiatrist
g. who are judged to be in need of urgent psychiatric treatment
h. who are unable to communicate adequately because of language problems or cognitive impairment
i. who live outside reasonable travelling distance

Table 6.13 Reasons for ineligibility at each stage of eligibility assessment (reasons are not exclusive) (n=282)

Ineligibility criterion	At SCID interview n=162	At phone eligibility assessment n=82	At face-to-face eligibility assessment n=79
Expected survival of less than 6 months	19	5	2
Uncontrolled medical condition	0	2	0
Feels physically too unwell	0	7	5
Comorbid psychiatric diagnosis	10	4	2
Current alcohol or substance misuse	12	4	3
Chronic Depression	62	6	4
Receiving current psychological/psychiatric treatment	33	12	1
High suicide risk	31	2	0
Communication problems	0	2	2
Too far to travel	7	26	2
SCL-20 <1.72	0	6	64
*Other**	13	17	3
No data	1	0	0

*MDD of borderline 1 month (14); starting Ribavirin treatment (1); antidepressants contra-indicated (1); previous non-adherence to treatment programmes (1); not able to take time off work to attend for trial treatment (1); recently bereaved (2); discharged from Oncology services (6); about to start intensive anti- cancer treatment (2); out of country for next 6 months (1); can't attend as full-time carer (1); recruitment stopped (3).

Medical exclusion (a, b, c)

Survival: Of the 660 patients identified with MDD, 26 patients were deemed by their cancer specialist to have an expected survival of less than 6 months.

Comorbid uncontrolled/complicating medical problem: Medical problems assessed as uncontrolled or complicating (uncontrolled heart condition and unstable diabetes) were found in 2 cases.

Too ill to participate because of the cancer or its treatment: 12 patients considered themselves too frail or unwell.

Clustering of reasons did not occur within the medical exclusion criteria but occurred with 'feeling too ill' and 'feeling the travel would be too burdensome'.

Psychiatric exclusion (d, e, f, g)

Of the 660 patients with MDD, the most common exclusion reason at this stage was a reported history of more than 2 years of continuous depressive symptoms, defined as chronic depression. Clustering of ineligibility reasons occurred in all the criteria of psychiatric exclusion.

Co-morbid psychiatric condition or substance/alcohol misuse: 16 patients were excluded due to previously diagnosed co-morbid psychiatric conditions (eating disorder 3; chronic anxiety disorder 2; dementia 2; obsessive compulsive disorder 2; cognitive impairment due to Parkinson's 1; depressive psychosis 1; agoraphobia 1; bipolar affective disorder with obsessive compulsive disorder 1; chronic and severe somatisation disorder 1; schizoid personality 1; personality disorder 1), 19 patients had a current problem with alcohol abuse of which 3 patients also had a current problem with drug or substance misuse.

Continuous depression for more than 2 years prior to the SCID diagnosis of MDD: 72 patients were assessed with chronic depression.

Active treatment from a psychiatrist/psychologist: 46 patients were being treated for their depression and/or other psychiatric diagnoses by mental health specialists.

Requiring urgent psychiatric referral: Of the patients assessed for trial eligibility, 33 patients were assessed as having a suicide risk high enough to warrant immediate

attention. For these patients, their GP was informed and their care was managed from primary care services.

Exclusion other reasons (h, i, and 'other')

Four patients were excluded due to communication problems and 35 patients felt unable to travel to the Research Centre for the trial. Other exclusion reasons are tabled above, which included one patient who was receiving a chemotherapy trial agent. Following discussion with the relevant pharmaceutical company the patient was excluded due to possible drug interaction with antidepressant medication.

Failure to meet study criteria for MDD on the SCL-20 depression measure

Of the patients assessed with the SLC-20 questionnaire, 70 patients were found not to meet the study criteria SCL-20 score for MDD of ≥ 1.72.

Two patients were never assessed for trial eligibility due to a system error.

Refusals

Numbers of and reasons for refusals at all stages of screening and assessment are shown in Figure 6.2 and Table 6.14. All reasons are exclusive.

Table 6.14 Reason for trial refusal at each stage of assessment (reasons are exclusive) (n=134)

Refusal reason	At SCID interview n=34	At phone eligibility assessment n=95	At face-to-face eligibility assessment n=5
Doesn't want to do it/not interested/doesn't feel it would help	16	27	0
Wants to work on it themselves/too many problems/too busy	10	26	1
No reason given	3	12	1
Doesn't feel depressed	0	13	1
Wants to see other HCP/would rather see GP/receiving GP care already	3	7	2
*Other**	2	10	0

*Worried about confidentiality (4); feels too unwell (3); doesn't like hospitals (3); too deaf (1); GP advised patient not to take part (1).

Of those approached about the trial following a positive diagnosis on the SCID interview, 34 patients refused trial information. Of the 463 patients proceeding to the 2nd stage of eligibility assessment, the telephone assessment stage, 87 patients refused the eligibility assessment. The most common refusal reason given was either 'not interested' or 'doesn't want to take part in the trial'. Of the 284 patients who completed the final stage of eligibility assessment five patients refused. The percentage of patients who refused trial participation was 20% (134/660).

The characteristics of those who refused were compared with the 200 trial participants showing only a marginal difference between them in cancer type. More patients with testicular, prostate or urological cancers participated in the trial, whereas more haematology patients refused trial participation, see Table 6.15. On the

characteristics examined, the sample of patients who took part in the trial was representative of the total sample of trial eligible patients diagnosed with MDD.

Table 6.15 Demographic characteristics comparing trial participants and refusers. Number (percent) is shown except when specified.

Variable	Refusers (n = 134)	Trial participants (n = 200)
Patient characteristics		
Age in years Mean (sd)	59.0 (14.2)	56.6 (11.9)
Female	95 (71%)	141(70.5%)
Cancer type		
Breast	54 (40%)	87 (43.5%)
Testicular/prostate/urology	17 (13%)	42 (21%)
Colorectal	11 (8%)	13 (6.5%)
Gynaecological	22 (17%)	31 (15.5%)
Haematological	22 (17%)	19 (9.5%)
Lung	2 (1%)	4 (2%)
Melanoma/Sarcoma	6 (4%)	4 (2%)
Scottish Index of Multiple Deprivation score[1]	12.87	13.98
Median (range)	(1.54, 71.83)	(1.09, 76.94)
Missing		1

[1] *Scottish Executive (2004)*

Two hundred patients agreed to trial participation, were consented and randomised. Randomisation was in almost all cases performed on the same day of consenting. On

three occasions, the trials unit were unable to provide a randomisation service that day and in these cases all patients were randomised within 3 days of completing the trial consent and baseline questionnaires.

Final sample size

Patients were recruited into the study between 16th October 2003 and 19th December 2006. Recruitment was stopped when 200 eligible patients who had given consent to participate in the study, had been randomised. Full descriptive data was collected on these patients, who represented 59% (200/337) of the potentially eligible patients.

DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE AT BASELINE

Gender

It can be seen in Table 6.16 that the sample was predominantly (70.5%) female with a mean age of 56.6 years.

Living arrangements

The majority (75%) of patients were living with someone, either partner, children or friend. Only 50 patients (25%) were living alone.

Table 6.16 Demographic characteristics of the sample (n=200)

Variable	Number (percent) unless indicated
Age (years)	
Mean (SD)	56.6 (11.9)
Gender	
Female	141 (70.5)
Marital status	
Married/cohabiting	132 (66)
Single	22 (11)
Currently divorced/separated	33 (16.5)
Widowed	13 (6.5)
Living situation	
Living alone	50 (25)
Living with partner	131 (65.5)
Other living arrangement	19 (9.5)

Deprivation

The Scottish Index of Multiple Deprivation (SIMD) Score (Scottish Executive 2004) was used to determine the overall deprivation based on the five domains of income, employment, health, education and access. The SIMD score for the sample was 13.98, indicating that almost 14% of the sample were deprived, see Table 6.17.

Employment

The pre-illness occupations of the patients covered a range of jobs; 16% were in professional positions and 14% were unemployed, see Table 6.17.

Table 6.17 Deprivation and employment characteristics of sample (n=200)

Variable	Number (percent)
Employment	
Professional	32 (16)
Clerical	20 (10)
Manual	32 (16)
Unemployed	28 (14)
Student	2 (1)
Housewife/husband	6 (3)
Medically retired	8 (4)
Retired	72 (36)
Scottish Index of Multiple Deprivation Score[1] Median (range)	13.98 (1.09, 76.94)

[1] *Scottish Executive (2004)*

ILLNESS CHARACTERISTICS OF THE SAMPLE AT BASELINE

Depression

The median duration of depressive symptoms prior to assessment was 7 months although the range extended from 2 to 24 months and for 34.5% (69/200), this was their first episode of depression, with 45.5% (91/200) reporting having had one previous episode and 20% (40/200) reporting having had more than one previous episode of depression. 37% (72/200) of the sample had spoken to their GP about their current episode of depression. Of these, 75% (54/72) had been offered an antidepressant, of which 69% (37/54) had accepted a prescription and were taking them, although only 69% (35/54) of patients had been prescribed an antidepressant deemed to be prescribed at a therapeutic level i.e. the minimum effective dose (adequacy of dose defined by the dose specified in the British National formulary (www.bnf.org) taking into account evidence by Furukawa et al (2002) suggesting that tricyclic antidepressant drugs may be effective at a lower dose of 75mg, (see Table 6.18).

Table 6.18 Baseline depression characteristics of sample (n=200)

Variable	Number (percent) unless indicated
Duration of current depressive episode in months	
Median (range)	7 (2, 24)
Previous episodes of depression	
Mean (sd)	0.9 (0.82)
Median (range)	1 (0-4)
Current treatment	
Spoken to GP about current episode (no data = 3)	72 (37)
Offered antidepressant medication (no data = 2)	54 (27)
Prescribed antidepressant medication	43 (22)
Prescribed therapeutic dose (no data = 1)	35 (18)
Taking full therapeutic dose prescribed	31 (16)

Depression Scores

The median for HADS scores for the sample was 21 ranging from 9 to 39. Scores of less than 15 were for patients who had endorsed the question on the PHQ concerning presence of suicidal ideation and were therefore included in the sample eligible for further assessment. The number of symptoms endorsed from the SCID interview ranged from 3 to 9 with the median being 6. One patient with only 3 SCID items was

included in the sample diagnosed with MDD as she had endorsed the two core items of depressed mood and anhedonia, had previously repeatedly scored highly on screening questionnaires and was therefore felt to have probable MDD. Scores on the SCL-20 (completed within 1 month of the initial SCID interview) ranged from 1.75 to 3.55 with a median score of 2.35, (see Table 6.19).

Table 6.19 Baseline depression scores of sample (n=200)

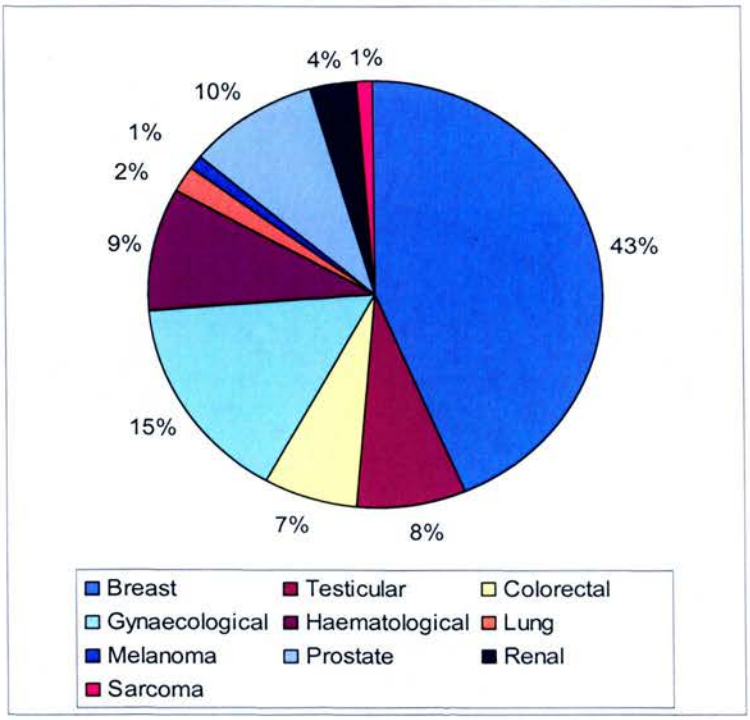
Variable	Median (range)
Total HADS score (0 - 21)	21 (9, 39)
Number of SCID symptoms (min 5, max 9)	6 (3, 9)
SCL-20 (0 – 4.0)	2.35 (1.75, 3.55)

Cancer

Cancer type

Of the sample, the majority of patients had breast cancer 43.5% (87), with the remainder having the following cancers: gynaecological (ovary, uterus and cervix) 15.5% (31); haematological 9.5% (19); prostate 9.5% (19); testicular 8% (16); bowel 6.5% (13); renal 3.5% (7); lung 2% (4); melanoma 1% (2); and sarcoma 1% (2), (see Figure 6.3).

Figure 6.3 Cancer type of sample (n=200)



Cancer characteristics

The median interval since the most recent cancer diagnosis, taken from the time of trial entry, was 18.4 months with a mode of 7 months and of the sample, a small number 8.5% (17) had been diagnosed with another primary cancer in the past. A large number of patients 66% (132) were classed as disease free, a small number 21% (42) had local disease and a smaller number had metastatic disease 13% (26). A large proportion of the patients were not receiving active treatment and were currently being monitored for recurrence or disease progression 83% (166) with a small proportion on active anti-cancer treatment 17% (34), of which 29% (10) were receiving radiotherapy, 56% (19) were receiving chemotherapy and the remaining 15% (5) were receiving a combination of radiotherapy and chemotherapy (see Table 6.2). Active anti-cancer treatment did not include hormone treatment.

Table 6.2 Baseline cancer characteristics of sample (n=200)

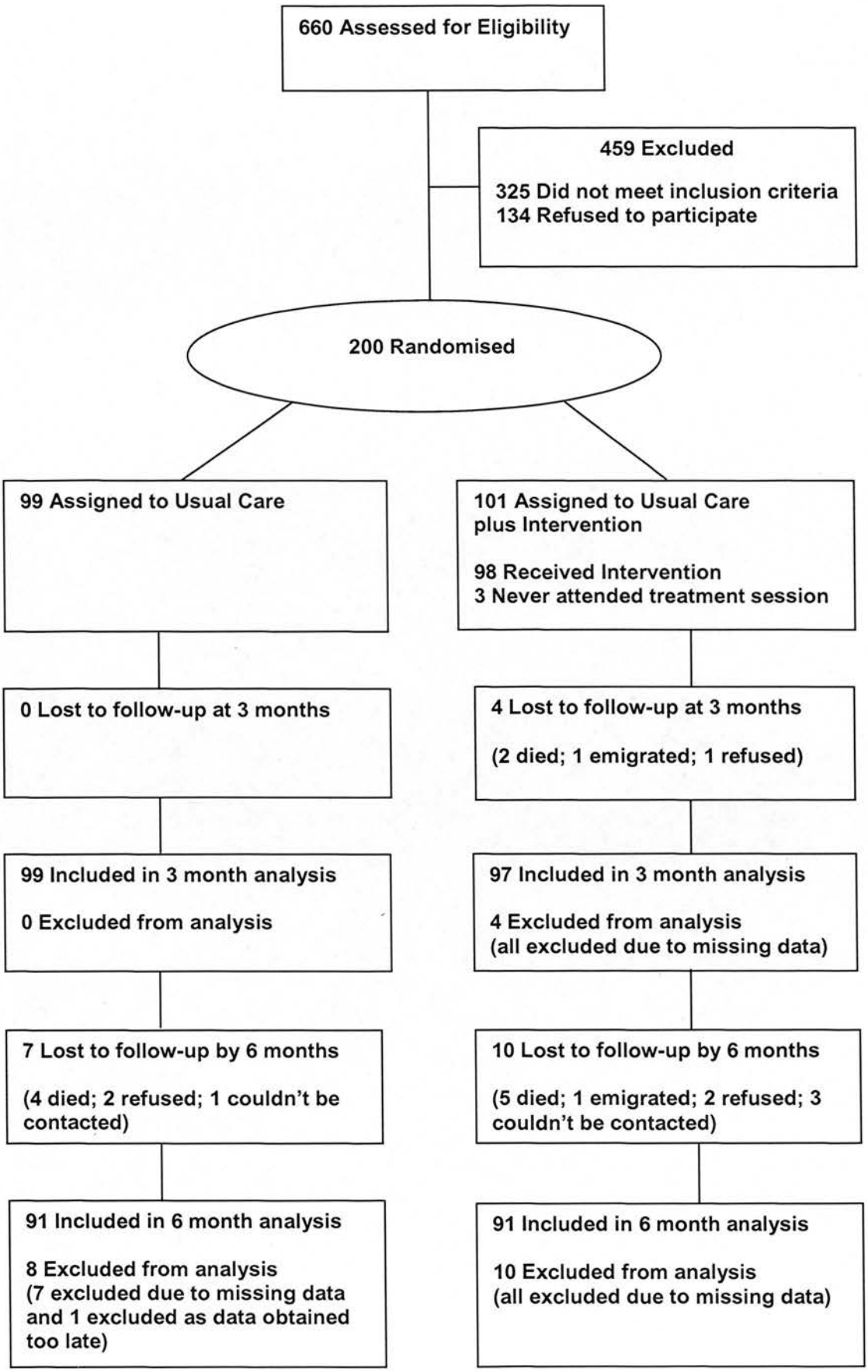
Variable	Number (percent) unless indicated
Cancer diagnosis	
One primary cancer diagnosis	183 (91.5)
Two primary cancer diagnoses	17 (8.5)
Length of diagnosis (months)	**Median (range)**
Time since first primary cancer diagnosis	23.7 (0.8, 219.5)
Time since most recent cancer diagnosis*	18.4 (0.7, 219.5)
Extent of disease	**Number (percent) unless indicated**
Disease free	132 (66)
Local disease present	42 (21)
Metastases	26 (13)
Treatment stage	
Pre-treatment/under investigation	22 (11)
Receiving active treatment	34 (17)
Being monitored/ post-treatment assessment	145 (72.5)
Anti-cancer treatment	
Receiving radiotherapy	10 (5)
Receiving chemotherapy	19 (9.5)
Receiving both	5 (2.5)

* 'most recent cancer diagnosis' refers to diagnosis of a new cancer, a recurrence or metastases.

FLOW OF PATIENTS THROUGH THE TRIAL

The progress of patients through the trial is shown in Figure 6.4, which is based on that recommended in the CONSORT statement on the reporting of trials (Moher et al 2001).

Figure 6.4 Flow of patients though the trial and follow up (CONSORT diagram)



DEMOGRAPHIC CHARACTERISTICS OF THE TREATMENT GROUPS AT BASELINE

Randomisation was performed using a random element in the allocation procedure of 0.75:0.25 to yield two treatment groups, 99 patients in the usual care group and 101 in the usual care plus intervention group. The randomisation was also restricted using a method called minimisation. The characteristics of the randomised groups are described in the Tables 6.21 to 6.27. There are no substantial differences between the groups other than in employment characteristics and current treatment for their depression. More patients in the usual care group were working in clerical jobs and more patients were unemployed. More patients in the usual care group had consulted their GP and were receiving antidepressant medication for their current depressive episode.

Table 6.21 Demographic characteristics of the treatment groups at baseline. Number (percent) is shown except when specified.

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Patient characteristics		
Age in years Mean (sd)	56.6 (12.3)	56.6 (11.4)
Female	71 (72)	70 (69)
Marital status		
Married or cohabiting	67 (68)	65 (64)
Single	10 (10)	12 (12)
Divorced/separated	17 (17)	16 (16)
Widowed	5 (5)	8 (8)
Living situation		
Living alone	24 (24)	26 (26)
Living with partner	69 (70)	62 (61)
Other living arrangement	6 (6)	13 (13)

Table 6.22 Deprivation and employment characteristics of the treatment groups at baseline. Number (percent) is shown except when specified.

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Employment		
Professional	13 (13)	19 (19)
Clerical	13 (13)	7 (7)
Manual	14 (14)	18 (18)
Unemployed	19 (19)	9 (9)
Student	2 (2)	0 (0)
House wife/husband	2 (2)	4 (4)
Medically retired	3 (3)	5 (5)
Retired	33 (33)	39 (39)
Scottish Index of Multiple Deprivation Score[1] Median (range)	14.87 (1.81, 76.94)	12.66 (1.09, 76.94)

[1] *Scottish Executive (2004)*

ILLNESS CHARACTERISTICS OF THE TREATMENT GROUPS AT BASELINE

Depression

There were no substantial differences in the depression characteristics between the groups: duration of the current depressive illness prior to assessment, number of previous episodes of depression, but there were some small differences in treatment

received. the number of patients who had spoken to their GP, been offered and prescribed an antidepressant, prescribed an antidepressant deemed to be prescribed at a therapeutic level, and taking the prescribed antidepressant, was slightly higher in the usual care group, (see Table 6.23).

Table 6.23 Depression characteristics of the treatment groups at baseline. Number (percent) is shown except when specified.

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Duration of current depressive episode in months		
Median (range)	6 (2, 24)	8 (2, 24)
Previous episodes of depression		
Mean (sd)	0.94 (0.81)	0.85 (0.83)
Median (range)	1 (0-3)	1 (0-4)
Current treatment		
Spoken to GP about current episode	40 (42) (no data = 3)	32 (32)
Offered antidepressant medication	23 (24) (no data = 2)	31 (31)
Prescribed antidepressant medication	25 (25)	18 (18)
Prescribed therapeutic dose	20 (20) (no data = 1)	15 (15)
Taking full therapeutic dose prescribed	18 (18)	13 (13)
Duration of current depressive episode in months		
Median (range)	6 (2, 24)	8 (2, 24)

Depression scores

There was no substantial difference at baseline between the treatment groups in the mean HADS scores, the mean number of SCID symptoms endorsed or mean SCL-20 scores, as shown in Table 6.24.

Table 6.24 Depression scores of the treatment groups at baseline. Numbers shown are median scores (range).

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Total HADS score (0 - 21)	21 (9,39)	21 (13,37)
Missing	3	4
Number of SCID symptoms (min 5, max 9)	6 (3, 9)	7 (4, 9)
SCL-20 (0 – 4.0)	2.25 (1.75, 3.25)	2.35 (1.75, 3.55)

Cancer

Cancer type

There was no substantial difference in cancer types between the groups, (see Table 6.25).

Table 6.25 Cancer type of the treatment groups at baseline. Number (percent) is shown except when specified.

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Cancer type		
Breast	44 (44)	43 (43)
Gynaecological (ovary, uterus, cervix)	15 (15)	16 (16)
Haematological	10 (10)	9 (9)
Prostate	9 (9)	10 (10)
Testicular	8 (8)	8 (8)
Bowel	6 (6)	7 (7)
Renal	3 (3)	4 (4)
Lung	1 (1)	3 (3)
Melanoma	1 (1)	1 (1)
Sarcoma	2 (2)	0 (0)

Cancer characteristics

There was no substantial difference in number of primary cancers, duration of diagnosis, extent of disease and treatment stage between the groups, (see Table 6.26).

Table 6.26 Cancer characteristics of the treatment groups at baseline. Number (percent) is shown except when specified.

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
Cancer diagnosis		
One primary cancer diagnosis	89 (90)	94 (93)
Two or more primary cancer diagnoses	10 (10)	7 (7)
Length of diagnosis (months)		
Time since first primary cancer diagnosis Median (range)	26.7 (2, 219.5)	22.4 (0.8, 172.6)
Time since most recent cancer diagnosis* Median (range)	21.5 (0.7, 219.5)	15.8 (0.8, 161.8)
Extent of disease		
Disease free	67 (68)	65 (64)
Local disease present	22 (22)	20 (20)
Metastases	10 (10)	16 (16)
Treatment stage		
Pre-treatment/under investigation	17 (17)	4 (4)
Receiving active treatment	15 (15)	19 (19)
Being monitored/ post-treatment assessment	67 (68)	78 (77)
Anti-cancer treatment		
Receiving radiotherapy	3 (3)	7 (7)
Receiving chemotherapy	10 (10)	9 (9)
Receiving both	2 (2)	3 (3)

* 'most recent cancer diagnosis' refers to diagnosis of a new cancer, a recurrence or metastases.

Subsidiary outcome measures in the treatment groups at baseline

Similarly an examination of the subsidiary outcome variables of the EORTC-QLQ-C30 scales, the 10 anxiety items of the SCL-90, the social support scale and single item measures of confidence and problem solving ability, (see Table 6.27) shows that there were no substantial differences between the groups on these variables at baseline.

Table 6.27 Subsidiary variables in each treatment group at baseline. Numbers shown are median scores (range).

Variable	Usual care only (n=99)	Usual care + Intervention (n=101)
EORTC-QLQ-C30 global health & quality of life scale (raw score 2 – 14; %age score 0-100)	42 (0, 92)	42 (0, 67)
EORTC-QLQ-C30 symptom scales		
Physical *(raw score 5 – 20; %age score 0-100)*	73 (7, 100)	67 (13, 100)
Role *(raw score 2 – 8; %age score 0-100)*	50 (0, 100)	50 (0, 100)
Cognitive *(raw score 2 – 8; %age score 0-100)*	50 (0, 100)	50 (0, 100)
Emotional *(raw score 4 – 16; %age score 0-100)*	33 (0, 83)	33 (0, 92)
Social *(raw score 2 – 8; %age score 0-100)*	33 (0, 100)	50 (0, 100)
EORTC-QLQ-C30 functioning scales		
Fatigue *(raw score 3 – 12; %age score 0-100)*	56 (11, 100)	56 (11, 100)
Pain *(raw score 2 – 8; %age score 0-100)*	33 (0, 100)	33 (0, 100)
SCL-90 anxiety items (0 – 4.0)	1.3 (0.0, 3.7)	1.5 (0.0, 3.9)
Coping measures		
Confidence (0-10)	5 (0, 10)	5 (0, 10)
Support (2-8)	7 (2, 8)	6 (2, 8)
Problem solving Q3 (1-4)	3 (1, 4)	3 (1, 4)
Problem solving Q4 (1-4)	3 (1, 4)	3 (1, 4)
Problem solving Q5 (1-4)	2 (1, 4)	2 (1, 4)

THE TREATMENTS

Administration and quality assurance of the treatment

Treatment compliance

All the patients who had agreed to be randomised in the trial and who were offered the additional trial intervention initially accepted it. Three patients later declined attending the problem-solving session component of the intervention. All patients allocated to usual care alone also accepted this.

All patients completed an adequate number of sessions in that all completed at least two sessions (the minimum number of sessions deemed to be therapeutic). The minimum number of sessions attended was two and the median number was 7. For one patient the therapist went to very considerable lengths to avoid the patient dropping out of therapy. This is discussed further below.

By the end of their treatment programme, 60% of patients were fully compliant (had participated in and attended a full programme of sessions and were taking a therapeutic dose of an antidepressant). A further 32% were partially compliant (had either participated in and attended an adequate number of sessions or were taking a therapeutic dose of an antidepressant) and the remaining 8% were non-compliant (had neither attended for the minimum sessions protocol requirement nor were not taking an antidepressant).

Treatment integrity

The two nurse therapists (Yvonne McIntosh and Jackie Whigham) treated a total of 81 patients (29 and 52 respectively) and I treated 20 patients. The relative efficacy of the three nurse therapists was determined by comparing the percentage of patients who met the three predetermined definitions of treatment response (50% reduction in the SCL-20 MDD score from baseline, no longer meeting DSM criteria for MDD and remission of depression as defined by SCL-20 score of <0.75) between therapists at 3 months, see table 6.28. However no statistical analysis was performed as the allocation of patients to therapists was not random.

Table 6.28 Depression scores of the intervention group at the 3 month follow up by therapist. Number (percent) is shown except when specified.

Proportions achieving a clinical treatment response at 3 months	**Y Mcl (n=29)***	**JW (n=52)**	**VS (n=20)**
50% reduction in SCL-20 score from baseline	14/27 (51.85) No data = 2	27/52 (51.92)	11/19 (57.89) No data = 1
Not longer meeting criteria for MDD diagnosis on SCID	21/27 (77.78) No data = 2	28/50 (56) No data = 2	15/19 (78.95) No data = 1
Remission of depression (SCL-20 score of <0.75)	11/27 (40.74) No data = 2	12/52 (23.07)	6/19 (31.58) No data = 1

*For one patient treated by Y Mcl, the SCL-20 data was obtained too late to be eligible for inclusion in the main trial analysis but has been included here.

Untoward events during treatment

No major untoward events occurred during the treatment. There were however a number of minor events across both trial groups over the 6 month trial period:

Intervention group

In the additional intervention group, one patient died from a sub-arrachnoid haemorrhage 16 days after trial entry having completed 3 treatment sessions and another patient died of cancer-related disease burden just before the three-month outcome assessment.

By 6 months, a further 4 events occurred, three cancer-related deaths and one hospital admission for suicide risk management. These events were reported as 'serious adverse events' to the Data Monitoring and Ethics Group and the patients' deaths were confirmed as unrelated to the trial treatment.

During therapy, two patients developed suicidal ideation, defined as thoughts of suicide with a plan. This was managed as part of their treatment with supervision from Professor Sharpe, consultant psychiatrist and principal investigator for the trial. One of these patients was referred by us after treatment in the trial to general psychiatry and was managed in the community by a community psychiatric nurse and the other patient was referred by her GP to the Liaison Psychiatry service at the local hospital and admitted to a psychiatric ward for treatment.

Sixteen patients reported suicidal thoughts at the 3 month follow-up assessment of which one had a plan. At 6 months 11 patients reported suicidal thoughts of which none reported any suicide plan.

Usual care group

In the usual care only group no events occurred in the first 3 months but by 6 months 4 patients had died of cancer-related causes and one patient had attempted suicide, for which she had been admitted to general emergency services at the local hospital and discharged to the care of her GP.

Eighteen patients reported suicidal ideation at the three-month follow-up, with 4 reporting a plan and at the six-month follow-up 18 patients reported suicidal thoughts with 3 reporting a plan.

For all patients in the trial reporting suicidal thoughts with a plan, their GP was informed immediately by phone and letters were sent to both their GP and Oncologist detailing the suicide risk assessment.

Experiences during treatment

Various issues emerged during the treatment. These were discussed at the weekly supervision meetings. The obstacles to effective use of the treatment differed between the patients and are mentioned in more detail below.

Engagement

Patients were not always entirely convinced that the problem-solving component could work for their problems. It sometimes took a number of sessions until they 'bought in' to the therapy. One patient had been sceptical throughout his entire treatment programme but admitted at his 3 month outcome assessment that with hindsight he had actually found the problem-solving technique and behavioural activation components very helpful.

Behavioural activation

Cultural differences sometimes required careful planning of activation. Body image following breast surgery had a profound impact on the activities these patients were willing to engage in. One patient wouldn't go out with her husband as she felt that he would be embarrassed by the deterioration in her physical beauty. Anti-cancer treatments also had an impact. One particular patient following chemotherapy wouldn't go outside because she was anxious that her wig would get blown away in the wind. Disease extent also had a major impact on the patient's ability to take part in physical activity due to fatigue, pain or physical disability. For these patients, less physical forms of behavioural activation were effective, such as resuming a previous non-physical hobby.

Antidepressant medication

A small number of GPs disagreed with the diagnosis, weren't willing to prescribe antidepressants or following recommendations were unwilling to change the medication or increase the dose. An expressed view by GPs was that 'it is normal for

cancer patients to feel depressed' and for this reason they felt that antidepressant prescribing was inappropriate or futile. Overall about half of the GPs did not fully collaborate with the model.

Patients themselves were initially reluctant to try antidepressant medication. Some patients wanted to try using the other components of the treatment first with the intention of adding in antidepressant drugs if their progress was slow. Some patients had misconceptions about the nature of antidepressant therapy. A commonly expressed view was that the medication was addictive or that they would become 'zombies'. One particular patient who was herself a trained health care professional declined antidepressants because she felt that her colleagues would know that she was taking them because of their side effects. However through problem-solving her mood and the effect it was having on her relationships she realised that her behaviour while depressed was more obvious to others than any side effects that may occur as a result of taking antidepressant medication.

One patient took a 'herbal' antidepressant prescribed by a herbalist which he very rigorously monitored and adjusted according to response. The patient made a very good recovery and even completed and passed her post graduate degree.

A few patients declined the antidepressant component of the treatment altogether and recovered in spite of this although recovery tended to be slower.

Cognitive change

The aims of cognitive change were to alter the patient's view of their depression as a 'natural and expected' consequence of having cancer to understanding their depression as a separate illness amenable to treatment, to broaden their understanding of depression and of their own depressive illness specifically in terms of their personal warning signs and trigger factors for relapse. Ultimately the change in cognition was aimed at making them more confident in their ability to manage their depression by equipping them with new skills to cope with concerns and problems that contribute to the development and/or maintenance of their depression.

The skill taught is a technique based on a problem-solving approach that involves the patient identifying a list of concerns and working on single concerns in a systematic way by setting goals related to the concern, then creating solutions to achieve the goal, considering the pros and cons of each solution, then choosing a solution to implement before the next therapy session. This constituted the patient's 'homework'.

The difficulty I encountered was that some patients failed to complete their homework and so progress was slow. When patients failed to complete homework, this was selected as the problem on which to focus, often resulting in either a plan for better time management or in redefining the goal set for the original problem. Patients with very chaotic thinking who reported always being busy found difficulties with generating solutions and with implementing their solution as homework. For some patients completing homework appeared overwhelming and in

these cases implementing the homework was broken down into steps that could be completed over a number of sessions.

For a few patients, the problem-solving technique seemed too difficult to learn even when simplified. For one particular woman problem-solving for the entire treatment programme was simplified to focusing on how to increase her physical activity using dusting as an example.

An interesting observation by all therapists was that white collar workers, and this seemed to apply to men in particular, had a tendency to make the problem-solving process too complicated and as a result had to be taught the skill of breaking problems into manageable chunks. One man who had been a company director even felt the need to 'reinvent' the problem-solving technique. This may have given him some control in the face of impending death.

Support

A commonly encountered reason for patients not willing to access support was the belief that they shouldn't burden family with more worries as they had already been burdened with their cancer illness.

Women tended to worry that admitting to family that they were depressed may mean losing their position within the family of caring for others or as the 'pillar' of the family. These assumptions were challenged within the problem-solving model by specifically addressing the issue of lack of support fairly early on in the treatment

programme thereby allowing the change to occur relatively slowly over the duration of the programme culminating in a specific plan for accessing support.

For a few patients asking for support felt to them like admitting they weren't coping when until then they had 'put on a brave face' and covered up any signs of distress. One man who had lived a very private life was unable to use support as he felt that this would disrupt his very valued privacy. Instead he chose to combine behavioural activation with social interaction but did not talk about himself or his concerns during these interactions.

Pre-illness personality and psychiatric morbidity

In some of the cases, it was clear that the patients would not generally be regarded as good candidates for a relatively brief psychological treatment although this had not been apparent or measurable in any sense at their eligibility assessment.

For a small proportion of the patients, deeply ingrained problems that clearly antedated the onset of their depression only emerged during therapy, such as childhood experiences of abuse. For these patients, it was evident that further treatment from a mental health specialist was recommended.

In another example, it became clear during the treatment of a man that he had a psychotic component to his depressive illness. He had persistent thoughts of suicide and when his care was transferred to community psychiatric services became very verbally abusive to his nurse therapist.

There were a few other patients who had problems with relationships indicative of personality disorder. For these patients, improvement was slow and minimal.

Non attendance for therapy sessions

In two cases persistent failure to attend for treatment sessions made delivering the number of sessions required within the defined time impossible.

For one patient, his reason was that he was a single parent of three children and his life was chaotic. For the other patient, her work came before her health and therefore work related meetings would always override therapy appointments.

Other treatments received during the six months of the trial

There were some differences between the groups in use of services. The use of GP services was higher in the intervention group, the difference being substantial in the 3 to 6 month period. This is reflected in the difference in use of antidepressant medication. At 3 months, the proportion of patients in the treatment group taking an antidepressant drug and taking it at a therapeutic level was double that of the usual care group. At 6 months the proportion of patients taking an antidepressant drug had reduced in the treatment group but had remained stable in the usual care group. Almost all patients were taking their antidepressant drug at a therapeutic dose at 6 months. More patients in the usual care group had received counselling and although the numbers referred to mental health specialists are small in both groups, the trend during the 6 months is for the usual care group to have consulted specialist mental

health services more than the treatment group. The 'consumption' of complementary and alternative medicine appeared slightly higher in the usual care group although the numbers were small. The range of therapies included in this category of service was diverse, comprising sacro-cranial therapy, spiritual and faith healing, reiki, reflexology, aromatherapy, crystal healing, colon hydrotherapy and acupuncture. The numbers are shown in Table 6.29.

Table 6.29 Use of general practitioner, other services and complementary and alternative medicine during the trial. Number (percent) is shown except when specified.

	Reported use of other sources of treatment		
Variable	**Usual care only (n=99)**	**Usual care + Intervention (n=101)**	**Whole group**
GP			
0-3 months	77/96 (80)	85/96 (89)	162/192 (84)
3-6 months	40/88 (45)	54/88 (61)	94/176 (53)
Mental Health Specialist			
0-3 months	7/95 (7)	3/96 (3)	10/191 (5)
3-6 months	10/87 (11)	7/89 (8)	17/176 (10)
Clinical Nurse Specialist			
0-3 months	13/95 (14)	83/96 (86)*	96/191 (50)
3-6 months	11/87 (13)	48/88 (55)	59/175 (34)
*Counselling***			
0-3 months	21/96 (22)	14/96 (15)	35/192 (18)
3-6 months	16/85 (19)	8/89 (9)	24/174 (14)
*Comp./Alternative Medicine****			
0-3 months	9/95 (9)	7/96 (7)	16/191 (8)
3-6 months	6/86 (7)	3/89 (3)	9/175 (5)
Taking antidepressant drugs			
At 3 months	37/99 (37)	72/97 (74)	109/196 (56)
At 6 months	34/91 (37)	58/91 (64)	92/182 (51)
Taking therapeutic level antidepressant drugs			
At 3 months	33/99 (33)	65/97 (67)	98/196 (50)
At 6 months	32/91 (35)	58/91 (64)	90/182 (49)

*Included some patients reporting seeing the trial depression nurse
** Counselling included attendance at Maggie's (a local drop-in cancer charity), counselling and breast care nurse
*** Alternative medicine included: sacro-cranial therapy; spiritual and faith healing; reiki, reflexology; aromatherapy; colon hydrotherapy; crystal healing; acupuncture.

MISSING DATA

Missing data for the primary outcome variable was minimal. Both the research assistants and I went to great efforts to maintain the patients' compliance with the assessments. Strategies to achieve this involved stressing the importance of delivering full and reliable outcome data to the funding charity at the baseline assessment together with sending out the self-report outcome assessment forms prior to the phone-based outcome interview, thereby enabling the research assistants to obtain any missing self-report data over the phone. This tended to be missing items of a questionnaire rather than whole missing questionnaire data. In 11 cases, patients were visited at home, hospital or hospice to recover outcome data.

The outcome data shown below are therefore complete unless otherwise stated. At three months, the only substantial missing primary outcome data was for four patients in the additional treatment group. Two patients had died, one patient had emigrated and one patient did not return the questionnaire. At six months the primary outcome data was unobtainable for a total of 17 patients. In the usual care group, four patients had died, two patients did not return their questionnaire and one patient could not be contacted. One of the patients who hadn't returned the questionnaire was however willing to describe the two core items of depressed mood and anhedonia to me when I visited him at home but declined to give any further information saying that he had been advised by his GP to withdraw from the trial. This assessment gave us sufficient detail about him to indicate that that there had been no substantial change in his condition since the previous assessment and this was used as secondary outcome data. In the treatment group 5 patients had died,

three patients could not be contacted, two patients did not return their questionnaire and one patient had emigrated. One further patient in the usual care group submitted her questionnaire data too late and this was therefore excluded from the analysis.

For the primary outcome of the self-report SCL-20, all 99 patients in the usual care group and 97 of the 101 patients in the treatment group were included in the analysis at 3 months and at 6 months 91 of the 99 patients in the usual care group and 91 of the 101 patients in the treatment group were included in the analysis. As described in the Methods Chapter, a sensitivity analysis was conducted for the 3 month primary outcome data imputing 'no change' by using baseline data for missing 3 month data.

At 3 months, data for the secondary outcome measure of the SCID assessment for MDD was missing for 2 patients in the usual care group and for 7 patients in the treatment group.

All analyses were conducted on a 'modified' intention-to-treat basis (as some outcome data was missing) and included all randomised patients for whom outcome data were available (196/200 at 3 months and 181/200 at 6 months).

OUTCOME AT THREE MONTHS

***Hypothesis**: Usual care plus a nurse-delivered, psychiatrist-supervised multi-component treatment intervention reduces symptoms of major depressive disorder in patients with cancer to a greater extent than usual care alone.*

The outcome assessments were performed at the times shown in Table 6.3.

Table 6.3 Time of trial outcome assessments

Mean (sd) time between trial entry and assessment (days)			
	Usual care only (n=99)	**Usual care + Intervention (n=101)**	**Whole group**
Assessment one (3 months/84 days)	82.95 (5.81)	82.49 (4.91)	82.72 (5.38)
Assessment two (6 months/168 days)	165.74 (11.04)	167.73 (7.32)	166.73 (9.39)

As can be seen, the assessments were carried out within 1 week either side of the calculated follow-up dates for the 3 month assessments and within 2 weeks of the calculated follow-up dates for the 6 month assessments as per protocol. There was no substantial difference between the groups in the mean number of days between trial entry and outcome assessments.

Outcome response

A fall in SCL-20 score is likely to be greater for those patients with high initial SCL-20 scores. All outcome analyses therefore included adjusting for baseline scores of the measure being analysed.

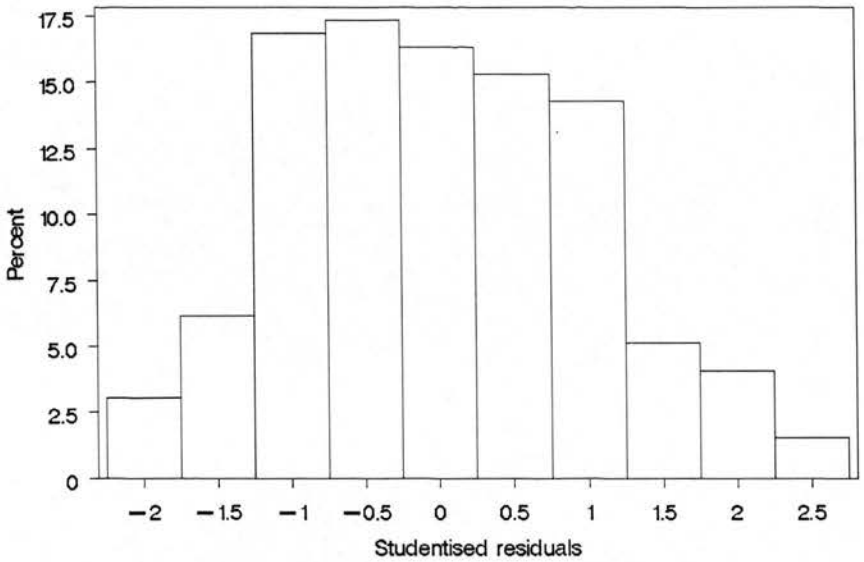
Primary trial outcome

The pre-determined primary outcome variable was the difference in mean scores on the self-report SCL-20 depression scale (range 0-4) and the pre-specified time point was 3 months after randomisation.

The chosen method for analysing the primary outcome was Analysis of Covariance (ANCOVA), using the 3 month SCL-20 score as the dependent variable whilst adjusting for the baseline SCL-20 score and the minimisation strata of age, gender, diagnosis and extent of disease.

For this method to be valid required the residuals from the fitted model to be approximately normal in distribution. A histogram of studentised residuals (Fig 6.5) when the ANCOVA model was fitted showed that they were reasonably normal in distribution.

Figure 6.5 Histogram of studentised residuals from ANCOVA model



For the analyses of the primary outcome, a P value of 0.05 (5% level) was taken to indicate statistical significance and in order to indicate the true range of the outcome value 95 percent confidence intervals were calculated.

The adjusted mean difference between the two treatment groups is presented in Table 6.31, together with 95% confidence intervals and corresponding P value. These show that the intervention had a statistically significant effect in reducing the SCL-20 score at three months, with an adjusted mean score 0.34 less than that for patients receiving usual care, with the true range of the value lying between 0.13 and 0.55.

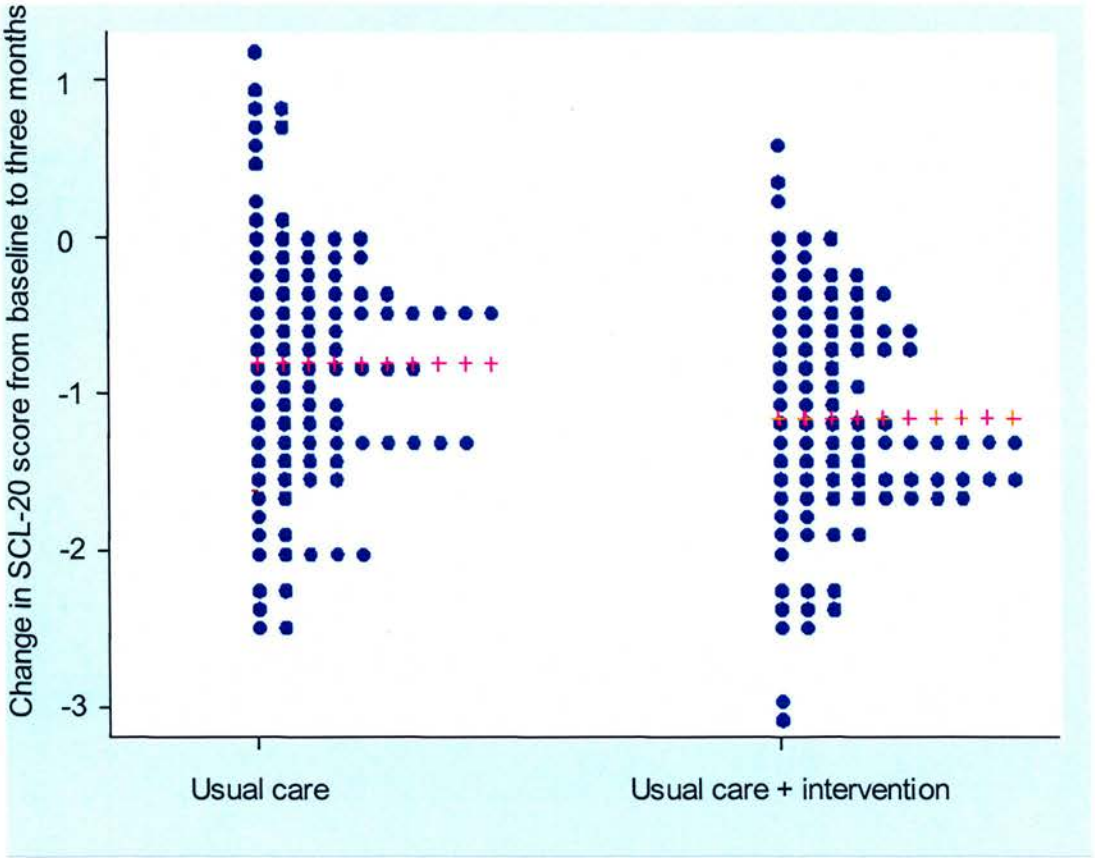
Table 6.31 Pre-specified primary outcome: Comparison of the SCL-20 score in the randomised groups at 3 months using ANCOVA, adjusting for minimisation variables (age, cancer diagnosis, extent of disease and gender) and baseline SCL-20 score.

	Usual care only (n=99)	**Usual care + Intervention (n=97)**	**Intervention effect* (95% CI)**	**p value**
	Mean (s.d.)	Mean (s.d.)		
SCL-20 score at three months	1.54 (0.80)	1.25 (0.77)	-0.34 (-0.55 to -0.13)	0.002

*The treatment means and standard deviations in the table above are raw values, but the intervention effect is adjusted for covariates.

Change in individual patient scores are shown in a dot plot (Figure 6.6). The mean for each group is shown by a line of plus symbols, and distances 1 standard deviation either side of the mean are marked by a dotted line. The graph shows a larger reduction in scores for the intervention group, as is reflected in the analysis of the primary outcome.

Figure 6.6 Change in SCL-20 score over first three months by treatment group.



The mean for each group is shown by the line of plus symbols.

Robustness of primary outcome to missing data

For the four patients with missing data at three months (who were all in the intervention group), it was assumed that their SCL-20 score had not changed since baseline. This assumption was fairly conservative, since for the intervention group only 6 patients of the 97 observed at three months had a score that was as bad as or worse than their baseline score (see Figure 6.6).

The previous analysis was repeated to see how this conservative estimate changed the results. The treatment effect was only made slightly smaller and was still statistically significant (see table 6.32). This suggests that the result of the primary outcome analysis was fairly robust to the missing data.

Table 6.32 Pre-specified primary outcome repeated imputing 'no change': Comparison of the SCL-20 score in the randomised group at 3 months using ANCOVA, adjusting for minimisation variables (age, cancer diagnosis, extent of disease and gender) and baseline SCL-20 score.

	Usual care only (n=99) Mean (s.d.)	**Usual care + Intervention (n=97)** Mean (s.d.)	**Intervention effect* (95% CI)**	**p value**
SCL-20 score at three months	1.54 (0.80)	1.29 (0.78)	-0.30 (-0.51 to -0.08)	0.007

*The treatment means and standard deviations in the table above are raw values, but the intervention effect is adjusted for covariates.

Standardised effect size

The adjusted difference in means (0.34) divided by the pooled standard deviation of the SCL-20 scores (0.8) gives an effect size (Cohen's d) of 0.43 with confidence intervals 0.15 to 0.72. This is a moderate treatment effect which will be discussed later when comparing the outcome of this trial with trials of similar interventions.

Subgroup analysis

To see whether the treatment effect was different in the subgroups of the study sample, an interaction term was fitted into the ANCOVA model. For the primary

outcome we looked at the 3 month SCL-20 modelled by baseline SCL-20, age, gender, cancer site, disease extent and treatment group, see table 6.33.

Table 6.33 Subgroup analysis for interaction effect

Interaction of treatment with:	Comparison of intervention effect for:	Coefficient (s.e.)	P-value
Age group	40-79 vs. <40	-0.15 (0.35)	0.650
	≥ 80 vs. <40	0.42 (0.74)	
Gender	Female vs. male	-0.00 (0.24)	0.985
Diagnosis	Colorectal vs. Breast	-0.03 (0.46)	0.396
	Gynaecological vs. Breast	-0.50 (0.32)	
	Other vs. Breast	0.04 (0.25)	
Disease extent	Local disease vs. disease free	-0.29 (0.27)	0.057
	Metastatic disease vs. disease free	0.63 (0.34)	

The only interaction that was even marginally significant was that between disease extent and treatment group. Whilst this may be a chance relationship, the result suggested that for patients with metastatic disease the effect of intervention on the SCL-20 at 3 months was smaller by 0.63 than in the disease-free patients, and the intervention reduced the SCL-20 at 3 months by 0.29 more in patients with local disease than in disease-free patients. The order of severity of these three categories of disease extent (disease free, local disease, metastases) was not reflected by the order of effect sizes; this, along with the p value slightly larger than 0.05 and the fact

that for each of the minimisation factors there were very small numbers in some of the strata, suggests that the result may not be particularly reliable.

Secondary trial outcome

The pre-determined secondary depression outcome variables were failure to meet the DSM1V criteria for Major Depressive Disorder; remission of depressive symptoms defined as a score of <0.75 on the SCL-20 depression measure; and a 50% reduction from baseline in the SCL-20 score. The pre-specified time point was 3 months after randomisation.

To account for multiple testing, secondary outcomes were considered only to be statistically significant if $p<0.01$. Treatment effects are all for the intervention group in comparison to the usual care group. Analyses of the secondary outcome measures were performed using logistic regression adjusting for the baseline measurement and minimisation factors. The exception to this was remission of MDD as defined by SCID interview: this included baseline SCL-20 score rather than SCID items endorsed since there is not a straightforward relationship between number of items endorsed and diagnosis of MDD. The SCL-20 baseline score was included so that some measure of baseline depression was taken into consideration.

In addition to having a significant effect on the mean SCL-20 score at three months, there was a statistically significant difference in proportions of patients achieving the pre-specified secondary outcomes between the groups as shown in Table 6.34. The intervention had a significant effect on the likelihood of a patient achieving a 50% reduction in SCL-20 between trial entry and three months, roughly doubling (95% CI

1.23 to 3.97) the odds, and trebling (1.38 to 6.27) the odds of achieving remission as defined by a score less than 0.75 on the SCL-20. This suggested that the statistically significant effect of treatment on the primary outcome was supported by an effect on clinically important criteria. The odds of not having MDD after three months, as assessed independently by the clinical diagnostic SCID interview, are increased by 2.76 (1.49 to 5.09) times on the intervention group, which corroborates the remission results from the self-report SCL-20 score.

Table 6.34 Pre-specified secondary depression outcomes: comparison of treatment groups at 3 months using Logistic Regression providing Odds Ratio as effect size, adjusting for baseline SCL-20 scores and minimisation variables; number (percent) with good outcome; and difference between the treatment groups

Outcome	Usual care only (n=99) n/N (%)	Usual care + Intervention (n=101) n/N (%)	Intervention effect (95% CI)	p value
Treatment response (50% reduction on SCL-20)*	34/99 (34%)	51/97 (53%)	2.21 (1.23 to 3.97)	0.008
Remission of MDD (<0.75 on SCL-20)	14/99 (14%)	28/97 (29%)	2.94 (1.38 to 6.27)	0.005
Remission of MDD (SCID)	44/97 (45%)	63/94 (67%)	2.76 (1.49 to 5.09)	0.001

* Achieved a reduction of 50% or more from their baseline SCL-20 score of ≥ 1.72

As the SCID remission of MDD is determined by an algorithm, some of the patients who were deemed in remission could nonetheless still display one or both of the core MDD symptoms of anhedonia and depressed mood. Therefore to illustrate remission

further, Table 6.35 below shows the proportions of patients defined as in remission but with persisting core depressive symptoms.

Table 6.35 Patients defined as 'in remission' according to SCID interview, yet still experiencing at least one core symptom of depression; number (percent) is shown

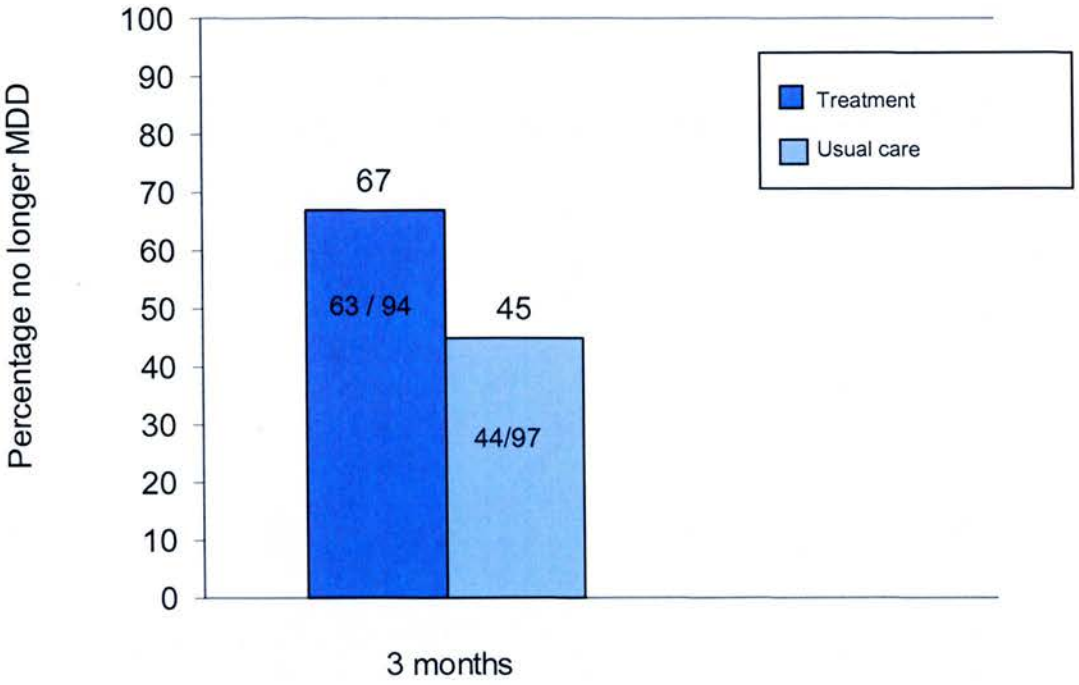
Outcome	Usual care only (n=44)	Usual care + Intervention (n=63)
SCID remission patients with depressed mood	6 (14)	4 (6)
SCID remission patients with anhedonia	3 (7)	3 (5)
SCID remission patients experiencing at least one of the core depressive symptoms	8 (18)	7 (11)

Absolute numbers were very similar between the two groups, though this translated to a lower proportion in the treatment group since there were more patients in SCID remission in this group.

A simple group comparison of outcome

Figure 6.7 shows that the difference between the treatment groups in the percentage of patients attaining a good outcome based on the clinical diagnostic interview at the 3 month follow up was 22%. This difference is clearly substantial and statistically significant.

Figure 6.7 Percentage of patients with remission on SCID interview at 3 months



In order to examine further the clinical significance of the result several additional calculations were made, see Table 6.36. These will be considered further in the Discussion chapter.

Standardised effect size

A standardised effect size (SES) is a scale-free measure of the relative size of the effect of an intervention and hence allows for comparison of relative size of effects from different studies. The difference in proportions attaining a good outcome was therefore translated to a standardised effect size. For binary outcome data this is termed the standardised mean difference (SMD) and is obtained using a multiple of

the log odds ratio (Chinn 2000). The standardised mean difference of the intervention based on SCID interview was 0.28.

Relative risk reduction

The effect of a treatment (RRR) can also be estimated by determining the relative risk reduction of a poor outcome (as defined by failure to achieve a clinical response at 3 months from baseline).

The relative risk reduction is calculated as the proportion with poor outcome in the usual care group, minus the proportion with poor outcome in the usual care + additional intervention group, divided by the proportion with poor outcome in the usual care group.

The RRR for the treatment effect based on clinical interview outcome assessment was: $55 - 33 / 55 = 40\%$

In other words, the additional intervention reduces the risk of persistent depressive symptoms at 3 months by 40%.

Absolute risk reduction

The absolute risk reduction (ARR) is calculated as the proportion with poor outcome in the usual care group minus the proportion with poor outcome in the usual care plus additional intervention group.

The ARR for the treatment effect based on clinical interview outcome assessment was 22%. This means that for every 100 patients enrolled in the additional intervention group, about twenty-two bad outcomes would be averted.

Number needed to treat

The number needed to treat (NNT) gives an estimate of the number of patients we would need to treat in order to prevent one bad outcome and is calculated as 1/ARR. So for the treatment effect based on clinical interview outcome assessment the ARR was 4.6. This means that we only probably have to treat 5 patients to prevent one patient having a bad outcome.

Table 6.36 Treatment effects calculated on clinically relevant outcome assessments

Outcome	Standardised effect size (SMD)*	Relative risk reduction (%)	Absolute risk reduction (%)	Number Needed to Treat (n)
Treatment response (50% reduction on SCL-20)	-0.22 (-0.38, -0.06)	27.8 (6.9, 43.9)	18.2 (4.6, 31.9)	5.5 (3.1, 21.8)
Remission of MDD (<0.75 on SCL-20)	-0.30 (-0.51, -0.09)	17.1 (3.8, 28.7)	14.7 (3.4, 26.1)	6.8 (3.8, 29.5)
Remission of MDD (SCID)	-0.28 (-0.45, -0.11)	39.6 (15.2, 57.1)	21.7 (7.9, 35.4)	4.6 (2.8, 12.6)

*Minus signs for SMD indicate a reduction in chance of the negative outcome, i.e. that the intervention group is better

Other secondary trial outcomes

The pre-specified secondary outcomes of anxiety, physical functioning and coping were also compared (Table 6.37 and 6.38).

Table 6.37 Secondary Outcomes: Comparison of treatment groups at 3 months using ANCOVA, adjusting for baseline SCL-20 scores, baseline measures of the outcome variable and minimization variables as appropriate

	Usual care only	**Usual care + Intervention**	**Intervention effect (95% CI)**	**p value**
	ANCOVA providing mean difference as effect size			
Physical functioning (0-100) Mean (sd)	N=92 67.6 (23.6)	N=91 66.8 (24.4)	1.0 (-3.4 to 5.5)	0.64
SCL-90 anxiety subscale (0-4) Mean (sd)*	N=93 0.97 (0.78)	N=91 0.78 (0.82)	-0.20 (-0.32 to -0.09)	0.001
Coping measure – confidence (0-10) Mean (sd)	N=93 5.9 (2.5)	N=91 6.6 (2.1)	1.02 (0.41 to 1.62)	0.001
Coping measure – support (2-8) Mean (sd)	N=92 6.7 (2.0)	N=91 7.2 (1.6)	0.65 (0.19 to 1.11)	0.006

* To achieve a normal distribution for ANCOVA the scores for this measure were square root transformed and the treatment effect cannot therefore be interpreted as actual scores.

Table 6.38. Secondary Outcomes: Comparison of treatment groups of proportions endorsing values representing good problem-solving skills from baseline to 3 months. Number (percent) is shown except when specified

	Usual care only N=99	**Usual care + Intervention N=101**	**Usual care only N=93**	**Usual care + Intervention N=91**
Problem solving (1-4)	At baseline n (%) scoring 3 or 4		At 3 months n (%) scoring 3 or 4	
Q3	63 (64)	52 (51)	58 (62)	58 (64)
Q4	70 (71)	71 (70)	68 (73)	70 (77)
Q5	47 (47)	46 (46)	53 (57)	63 (69)

There was a greater reduction in anxiety as measured by the SCL-90 anxiety subscale ($p=0.001$), (the scores for this measure were square root transformed to achieve a normal distribution and the treatment effect cannot therefore be interpreted as actual scores) but not in physical functioning ($p=0.643$).

For the coping measures of support and problem-solving, the functioning of the items was analysed prior to the results being made available. The purpose of this was to investigate whether the individual items of each of the support and problem-solving measures could be considered as a scale. Calculations of Cronbach's alpha indicated that the two items of support could be analysed together but not the problem-solving items. To avoid multiple analysis of the problem-solving measure, questions 3, 4 and 5 were chosen for the final analysis.

For the coping measures, a greater increase in confidence (p=0.001), use of support (p=0.006) and problem-solving ability was observed with the intervention which is consistent with some of the treatment effect being mediated by improving coping and problem-solving skills.

OUTCOME AT SIX MONTH FOLLOW UP

No testing was performed on the data at 6 months as the pre-specified primary outcome was at 3 months.

Secondary outcomes

Depression

The proportions achieving a good outcome on binary outcomes for the measures of depression are presented in Table 6.39. Of the182 patients included in the 6 month analysis, 65% (59/91) had a good outcome defined by a 50% reduction in SCL-20 score from baseline in the additional intervention group compared with the usual care group 38% (35/91). On the measure of remission defined as a score of less than 0.75 on the SCL-20 measure 45% (41/91) achieved remission in the additional treatment group compared to 15% (14/91) in the usual care group. On the clinical interview for diagnosis of MDD, 71% (64/91) no longer met the criteria for MDD in the additional treatment group compared to 55% (49/91) in the usual care group.

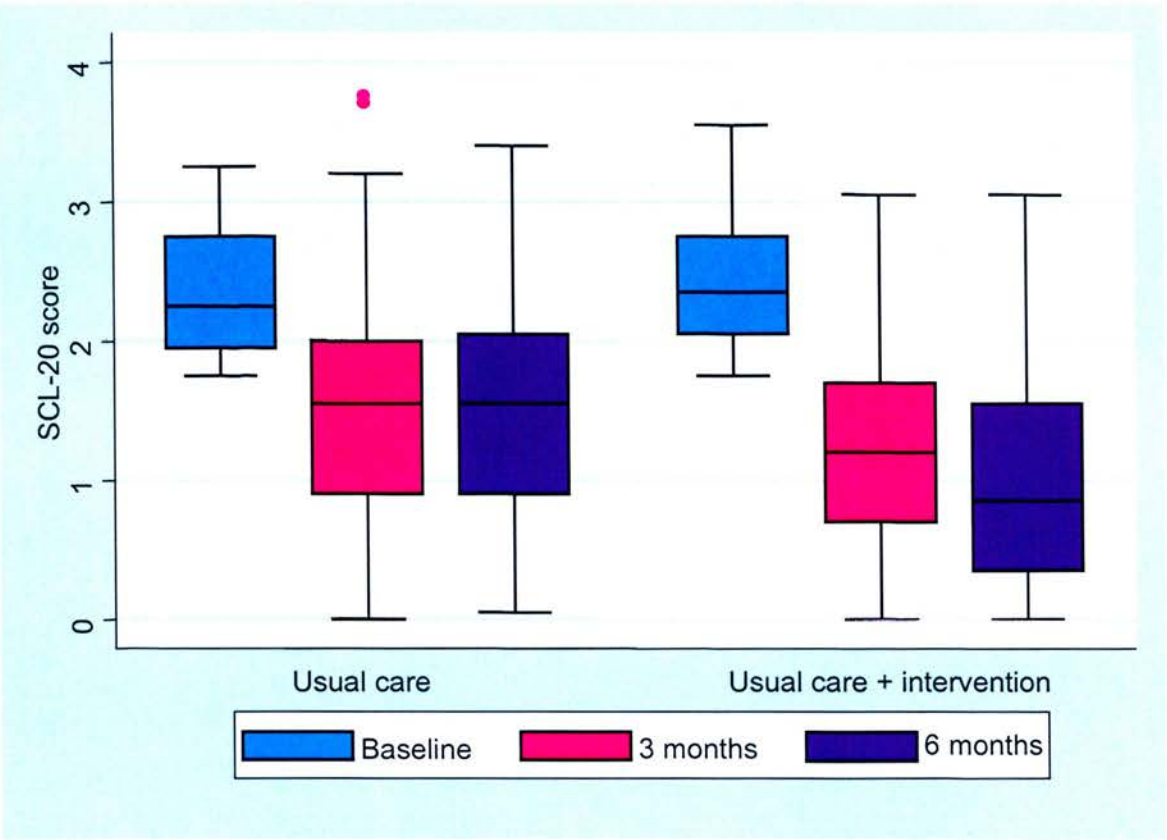
Table 6.39 Depression outcomes at 6 months; number (percentage) with good outcome (n=91 in each group)

Outcome variable	Usual care only	Usual care + Intervention
50% reduction on SCL-20 score	35 (38)	59 (65)
Remission (<0.75 on SCL-20 score)	14 (15)	41 (45)
Failure to meet criteria for MDD on SCID (data missing for 3 patients)	49/89 (55)	64/90 (71)

The proportion of patients having achieved a 50% reduction in SCL-20 score, from baseline, was higher at six months than at three months for both treatment groups. The proportion achieving remission had continued to increase from 3 months for the intervention group, whilst barely changing for the usual care group. As a result, the gap between the proportions in the two groups is quite wide. Proportions of patients no longer meeting the criteria for MDD had risen by similar amounts in both treatment groups.

Overall the difference between the treatment groups at 6 months was similar to that at 3 months. Although no statistical analysis was undertaken at 6 months, raw SCL-20 scores indicated a persisting treatment effect as presented in Figure 6.8.

Figure 6.8 Box plots of SCL-20 scores at 3 and 6 months by treatment group



The centre line represents the median and the boxes represent the interquartile range. The dots represent outliers.

Anxiety, physical functioning and coping

From table 6.4 the biggest differences between the groups in the proportion achieving either no change or an improvement appears in the measures of anxiety, physical functioning and confidence.

Table 6.4 Secondary outcomes at 6 months defined as no change or improvement on 3 month outcomes; number/total number (percentage)

Outcome variable	Usual care only *n/N (%)*	Usual care + Intervention *n/N (%)*
Physical functioning (0-100)	42/80 (53)	57/84 (68)
SCL-90 anxiety subscale	46/81 (57)	62/84 (74)
Coping measure – confidence	45/81 (56)	59/83 (71)
Coping measure – support	63/80 (79)	72/84 (86)
Problem solving (scoring 3 or 4)		
Q3	63/81 (77)	64/84 (76)
Q4	62/81 (77)	67/84 (80)
Q5	57/81 (70)	67/84 (80)

Satisfaction

Although the satisfaction rating was scored as a scale from 1-7, categories 1 and 2 represent 'no care received' and 'can't answer', while categories 3-7 rate quality of care as 'poor' (3), 'fair' (4), 'good' (5), very good (6) and 'excellent' (7). The results are shown in table 6.41.

Table 6.41 Satisfaction ratings at 6 months by treatment group; Number (percent) is shown except when specified

Satisfaction score	Usual care only n (%) N=85	Usual care + Intervention n (%) N=86
1	22 (26%)	1 (1%)
2	6 (7%)	3 (3%)
3	3 (4%)	0 (0%)
4	21 (25%)	7 (8%)
5	14 (16%)	7 (8%)
6	12 (14%)	27 (31%)
7	7 (8%)	41 (48%)

A quarter of the patients in the usual care group said that they had not received any care, compared to only one patient in the intervention group. Of those who had received care and were able to rate their care (categories 3-7) there is a clear difference of opinion between the two treatments, with usual care group showing a positively skewed distribution whilst the intervention group was negatively skewed. The satisfaction of patients receiving the intervention was greater than those receiving usual care.

TREATMENTS RECEIVED DURING THE TRIAL

After each outcome assessment, the progress of each patient was discussed with the supervising consultant psychiatrist. In all cases, after each outcome assessment, the

patient's GP and Oncologist were informed of the patient's progress. For those patients deemed to require additional intervention to that provided within the trial, a management plan was formulated in the multidisciplinary team, discussed with the patient and the appropriate management organised. This was in most cases notification to the GP of failure of the patient to improve and a request for the GP to review the patient's depression management. In 10 cases, a referral to psychology services at the Edinburgh Cancer Centre was made and in 2 cases, our recommendation to the patient's GP, of referral to psychiatric services was carried out. All other referrals were made independently by the GPs.

At each outcome assessment, patients were asked to report all the additional non-trial treatment they had received in the period since the last outcome assessment. The findings have been detailed previously in Table 6.29.

During the first 3 months of the treatment, three patients saw a mental health specialist after the end of the treatment sessions with the nurse. For other types of treatments, 14 patients had used counselling services of which the majority had used the local support centre, The Maggie Centre and 7 patients had received complementary or alternative medicine.

Between 3 and 6 months another 7 patients had seen a mental health specialist, another 8 had used counselling services and another 3 had used complementary or alternative medicine. These rates of service usage are less than those in the usual care arm as shown in Table 6.29. As the trial intervention is supplementary to usual care,

this confirmed that the patients in the usual care plus additional intervention group did not 'consume' more 'usual care' than those patients receiving usual care.

COMMENT

The additional nurse-delivered intervention was found in the efficacy trial to produce a substantially better outcome for depressive symptoms in patients with cancer and MDD at three months than that achieved by usual care alone. The large treatment effect seen in the primary outcome is substantiated by the secondary outcomes, providing robust evidence of efficacy. The six month data also suggest that the treatment effect is maintained.

CHAPTER 7: EXPLORATORY ANALYSIS AND PREDICTORS OF OUTCOME

Sections

Exploration of the process of clinical improvement with the additional nurse intervention
Comment

Exploration of the predictors of outcome
Comment

Exploration of treatment effect on functioning, quality of life and other key cancer-related symptoms

List of Tables

Table 7: Effect estimates of different covariates in a multivariate ANCOVA

Table 7.1: Exploratory analyses of EORTC QLQ-C30 scales: comparison of treatment groups

List of Figures

Figure 7: Scatter plot of change in SCL-20 score and change in confidence at 3 months by treatment group

Figure 7.1: Scatter plot of change in SCL-20 score and change in problem-solving Q3 at 3 months by treatment group

Figure 7.2: Scatter plot of change in SCL-20 score and change in problem-solving Q4 at 3 months by treatment group

Figure 7.3: Scatter plot of change in SCL-20 score and change in problem-solving Q5 at 3 months by treatment group

Figure 7.4: Scatter plot of change in SCL-20 score and change in social support at 3 months by treatment group

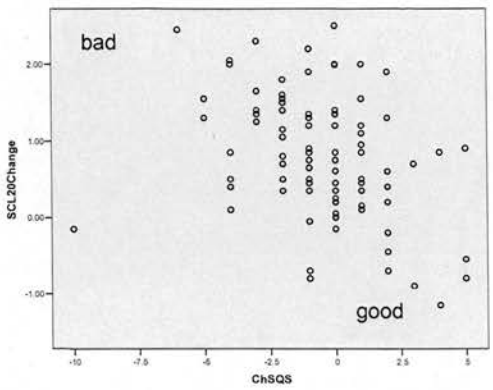
EXPLORATION OF THE PROCESS OF CLINICAL IMPROVEMENT WITH THE ADDITIONAL NURSE INTERVENTION

This trial provides robust evidence for the effect of the additional nurse-delivered intervention to usual care on a range of clinically relevant outcome variables. It cannot tell us what part of the complex intervention was effective in achieving this change and indeed the purpose of this trial was not to identify the 'effective ingredient'.

The question items used in this trial to measure a) the patients' confidence; b) their ability to cope with concerns and problems, and c) their access to and use of social support were used to understand the process of recovery within the talking therapy component of the intervention.

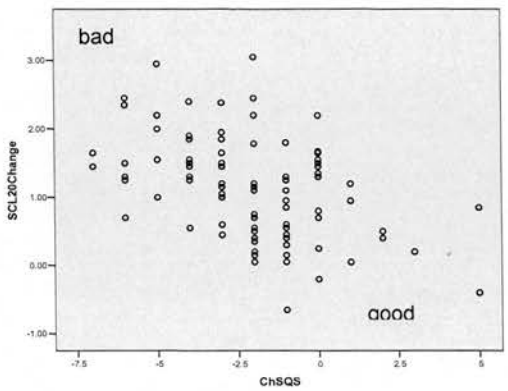
The hypothesis was that the additional nurse intervention improves outcome by a) increasing the patient's confidence to cope with concerns and b) teaching them a skill to tackle their concerns and c) increasing their access to and use of social support. This was explored in the following way: (1) To establish whether improvement in depression scores were mediated by improvement in aspects of confidence, coping and support, change in SCL-20 depression scores was plotted against change in scores for each of the coping items measured by treatment group. (2) To examine the significance of associations between changes in these variables with change in depression measure scores (SCL-20) in the additional intervention group and usual care group, correlations were sought using Spearman's Rank Correlation co-efficient, see Figures 7 – 7.4 below.

Figure 7 Association (scatterplot and Spearman's Rank correlation coefficient rho at 1% significance level) of change in SCL-20 depression score at 3 months and change in the confidence item score (I am confident in my ability to overcome or control this episode of depression)



Spearman's rho -0.368 (significant)

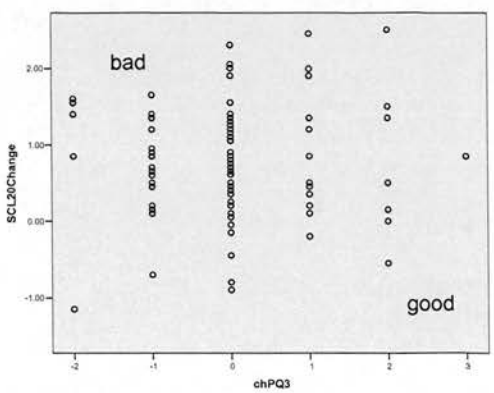
Scatter plot of Change in SCL-20 by change in Confidence at 3 months: Usual Care Group



Spearman's rho -0.394 (significant)

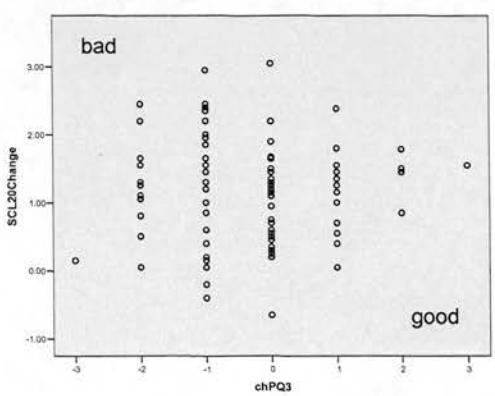
Scatter plot of Change in SCL-20 by change in Confidence at 3 months: Treatment Group

Figure 7.1 Association (scatterplot and Spearman's Rank correlation coefficient rho at 1% significance level) of change in SCL-20 depression score at 3 months and change in problem-solving item Q3 score (Q3. When I have a decision to make, I weigh the consequences of each option and compare them against each other)



Spearman's rho -0.084 (not significant)

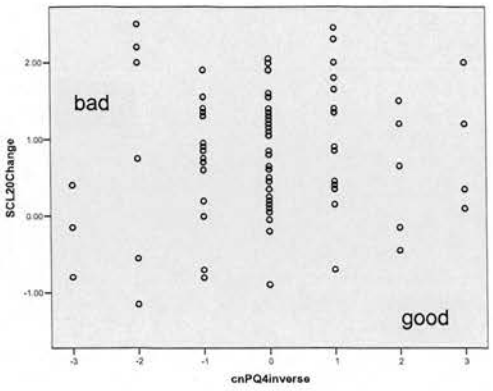
Scatter plot of Change in SCL-20 by change in Problem-solving Q3 at 3 months: Usual Care Group



Spearman's rho -0.054 (not significant)

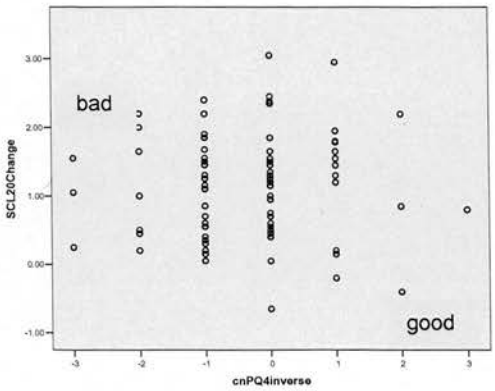
Scatter plot of Change in SCL-20 by change in Problem-solving Q3 at 3 months: Treatment Group

Figure 7.2 Association (scatterplot and Spearman's Rank correlation coefficient rho at 1% significance level) of change in SCL-20 depression score at 3 months and change in problem-solving item Q4 score (Q4. When I am attempting to solve a problem, I go with the first good idea that comes to mind)



Spearman's rho -0.080 (not significant)

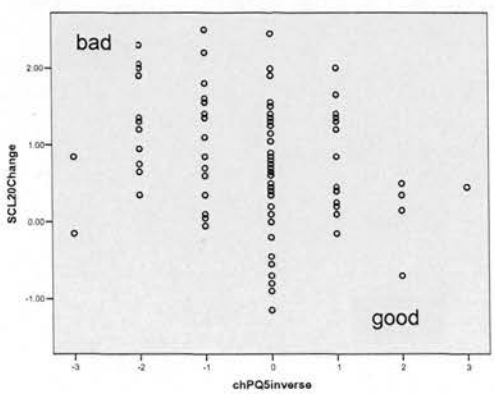
Scatter plot of Change in SCL-20 by change in Problem-solving Q4 at 3 months: Usual Care Group



Spearman's rho -0.102 (not significant)

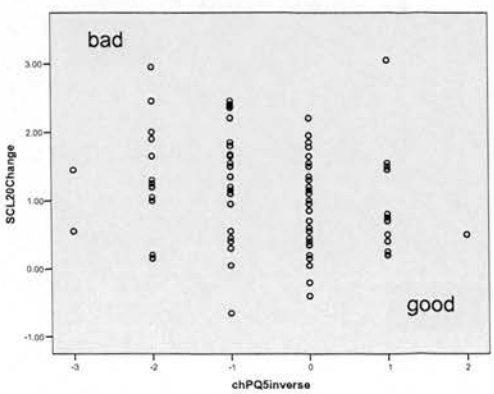
Scatter plot of Change in SCL-20 by change in Problem-solving Q4 at 3 months: Treatment Group

Figure 7.3 Association (scatterplot and Spearman's Rank correlation coefficient rho at 1% significance level) of change in SCL-20 depression score at 3 months and change in problem-solving item Q5 score (Q5. When a problem occurs in my life, I put off trying to solve it for as long as possible)



Spearman's rho -0.216 (not significant)

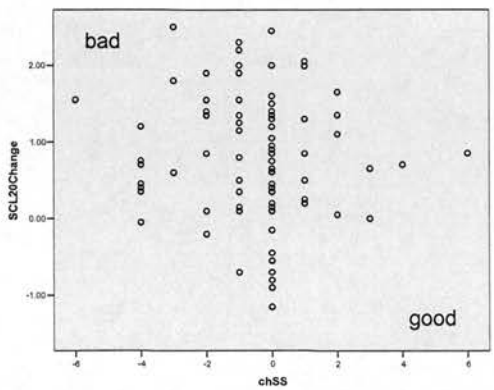
Scatter plot of Change in SCL-20 by change in Problem-solving Q5 at 3 months: Usual Care Group



Spearman's rho 0.2 (not significant)

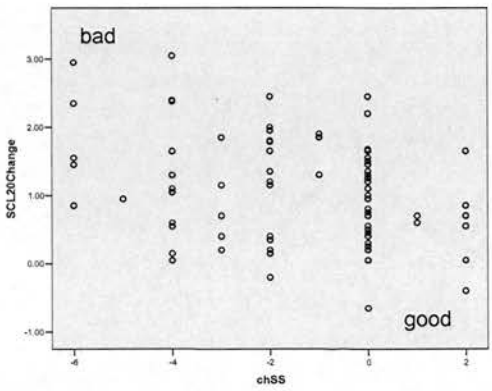
Scatter plot of Change in SCL-20 by change in Problem-solving Q5 at 3 months: Treatment Group

Figure 7.4 Association (scatterplot and Spearman's Rank correlation coefficient rho at 1% significance level) of change in SCL-20 depression score at 3 months and change in support scale (Amongst the people I know, there is someone I can go to for support + If I needed to, I would go to this person for support)



Spearman's rho -0.116 (not significant)

Scatter plot of Change in SCL-20 by change in Social Support at 3 months: Usual Care Group



Spearman's rho -0.195 (not significant)

Scatter plot of Change in SCL-20 by change in Social Support at 3 months: Treatment Group

No discernable pattern was noted other than with change in the measure of confidence. There was a statistically significant association between increasing confidence and improving depression scores with a stronger association in the treatment group.

Comment

The above findings suggest that a potential mediator of recovery from depression is increasing the patient's confidence in one's ability to overcome or control an episode of depression. The stronger effect seen in the treatment group provides preliminary evidence for the mechanism of the talking therapy being related to increasing patients' confidence in managing their depression.

EXPLORATION OF THE PREDICTORS OF OUTCOME

Four demographic and cancer-related minimisation factors were used for randomisation. No factors relating to the depressive illness were included. In order to inform future depression intervention trials, subgroup analysis was performed to identify predictors of outcome although this was not part of the pre-specified statistical analysis plan.

The number of previous episodes of depression and the length of current episode of depression were entered into the ANCOVA model to test whether they were predictive of good outcome.

Table 7 shows that the depression variables have an effect size in relation to the treatment of a similar order of magnitude to the treatment effect we obtained in the trial. Thus both depression variables were independent predictors of the SCL-20 score at three months at the 5% level and as such should be included as minimisation factors in any future trials to ensure reasonable balance between treatment arms so that any effect assigned to treatment is genuinely caused by the treatment.

The factors that were used in the trial for minimisation did not appear to have significantly influenced either the primary outcome (SCL-20) or the effect of treatment on the primary outcome, with the possible exception of extent of disease.

Table 7 Effect estimates of different covariates in a multivariate ANCOVA

Variable	Effect estimate (95% CI)	p value
SCL-20 at baseline	0.53 (0.3 to 0.77)	<0.0001
Treatment		
Intervention vs. control	-0.34 (-0.55 to -0.13)	0.002
Extent of disease		
Local vs. disease free	0.06 (-0.19 to 0.32)	
Metastatic vs. disease free	0.18 (-0.14 to 0.49)	0.538
Duration of current depressive episode		
More than a year vs. 1 year or less	0.33 (0.08 to 0.57)	0.009
Previous episodes		
≥ 1 vs. none	0.24 (0.02 to 0.46)	0.0305

Comment

Whilst I did not stratify on or adjust for these depression factors in analysing the trial, when using these three factors only as covariates (see table 7), the treatment effect is identical to that found in our planned analysis adjusting for age, gender, diagnosis and disease extent, which was reported at three months. Also of note is that the baseline comparability of the two trial treatment groups with respect to depression factors was satisfactory. Whether a greater imbalance would have affected the reported treatment effect cannot not be ruled out.

EXPLORATION OF TREATMENT EFFECT ON FUNCTIONING, QUALITY OF LIFE AND OTHER KEY CANCER-RELATED SYMPTOMS

The whole EORTC questionnaire was administered to participants upon entry to the trial, and again at three months. Only one scale was selected for analysis as a secondary outcome. There are, however, numerous symptom scales, many of which will not be analysed here since the treatment being evaluated is not expected to affect many cancer-related symptoms. The scales analysed were those examining functioning (role, emotional, social and cognitive), global health and quality of life, pain and fatigue.

The treatment effect shown in table 7.1 is the adjusted difference in mean scores at three months, from the ANCOVA. Treatment effects are all for the intervention group in comparison to the usual care group.

Table 7.1 Exploratory analyses of EORTC QLQ-C30 scales: comparison of randomised treatment groups using ANCOVA, adjusting for baseline score and minimisation factors

Variable (scale score range *)	Usual care Only Mean (sd) (N=93)	Usual care + Intervention Mean (sd) (N=91)	Treatment effect (95% CI)	P value
Emotional functioning (4-16)	50.18 (25.18)	63.95 (26.23)	15.68 (8.85 to 22.50)	<0.0001
Role functioning (2-8)	55.91 (34.20)	55.13 (33.49)	1.55 (-6.38 to 9.48)	0.7000
Social functioning (2-8)	55.56 (32.35)	58.61 (32.71)	3.41 (-3.92 to 10.73)	0.3602
Cognitive functioning (2-8)	58.42 (26.42)	64.47 (23.33)	8.81 (2.46 to 15.16)	0.0068
Pain (2-8)	37.81 (33.07)	36.81 (30.98)	-2.15 (-10.17 to 5.87)	0.5973
Fatigue (3-12)	55.44 (27.58)	49.69 (27.13)	-9.43 (-15.48 to -3.38)	0.0025
Global health & Quality of Life (2-14)	48.57 (23.24)	51.19 (21.43)	5.75 (-0.04, 11.53)	0.0515

* Scores range from 0 to 100; a higher score represents a higher level of the quantity being measured i.e. higher fatigue scores represent worse fatigue but higher functioning scores represent better functioning.

Table 7.1 shows small p-values for emotional functioning, fatigue and cognitive functioning, suggesting that there may be an effect of the intervention on each of these aspects. The direction of each of these differences favours the intervention.

Further investigation would be required to establish these results conclusively. Moreover, the effect sizes themselves are not large when compared to an increase of percentage made by one point increase in the raw score (the raw score varies according to the number, and range, of items in the scale). For emotional functioning, each point increase corresponds to an increase of 8.33 in the scale score; for cognitive functioning, each point corresponds to 16.67 and for fatigue, 11.11. Thus it is only the emotional functioning that shows, after adjustment, a mean difference of more than one point in raw scores.

DISCUSSION

Chapter 8: Summary of findings

Chapter 9: Methodological issues

Chapter 10: Other research relevant to the treatment model

Chapter 11: Implications of findings

Chapter 12: The current status of the collaborative care model approach to the management of MDD in cancer patients

CHAPTER 8: SUMMARY OF FINDINGS

Sections

Outcome

Process of improvement

Predictors of outcome

OUTCOME

The principal findings of the trial were that:

1. Patients who received optimised usual care plus the additional nurse-delivered multi-component intervention had a substantially better and statistically significantly better outcome on the pre-defined primary depression outcome measure than those who received optimised usual care only;
2. The treatment effect observed was fairly large with a number needed to treat of five (95% CI 3.1 to 21.8);
3. The benefit was sustained at the six month follow up.

Patients who had received the additional intervention also showed statistically significant improvements over usual care on the secondary outcome measures. These results serve to reinforce the effect on the primary outcome. However, no significant differences were observed on the measure of physical functioning between treatment groups although this is perhaps not a surprising finding given the nature of the comorbid illness of cancer.

PROCESS OF IMPROVEMENT

In a multi-component intervention it is not possible to conclude the mechanism by which patients improve. However, exploratory investigations of the mechanism by which the talking therapy component of the intervention improved depressive outcomes found a correlation between change in depression scores and change in confidence scores, suggesting that improvement in confidence may have had some influence on outcome.

PREDICTORS OF OUTCOME

Although exploratory, this analysis revealed some potential predictors. A history of one or more previous episodes of depression and a duration of current episode of depression of more than one year emerged as additional independent predictors of the SCL-20 score at three months. This suggests that these two factors in addition to baseline depression severity were predictive of good outcome.

CHAPTER 9: METHODOLOGICAL ISSUES

Sections

Definition of cases

Representativeness of the sample to the target population

Sample size

Eligibility and Randomisation

Specification of treatments given

Limitations of the outcome measurement

Clinical validity of the outcome measures

Blindness

Non-specific treatment effects

Active ingredient

Maintenance of treatment effect

Comment

The findings of this trial must be interpreted in the context of methodological limitations which I will discuss individually below.

DEFINITION OF CASES

Were the cases really MDD?

Despite on-going controversy about the use of the DSM criteria for diagnosing MDD in cancer patients, the inclusive diagnostic approach was used in this trial and it could be argued therefore that the cases were not MDD cases because of the significant somatic symptoms of the comorbid cancer. However the validity of these diagnoses was reinforced by using a measure of depression severity. Furthermore the prevalence found in this study is similar to those obtained by other studies using a variety of depression criteria and measures suggesting therefore that the diagnostic approach used in this trial correctly identified the severe end of the spectrum that is MDD.

REPRESENTATIVENESS OF THE SAMPLE TO THE TARGET POPULATION

Is the sample representative of patients with MDD in the target population?

Sampling bias in this trial was minimal and restricted only to those trial-imposed exclusion criteria that would 'risk' patient withdrawal or loss of data due to practical

reasons. The two criteria that require some consideration with regard to whether the sample relates accurately to the target population are patients who live outside reasonable travelling distance and those engaged in a course of intensive anti-cancer treatment.

Firstly, by excluding patients for reasons of travelling distance, in Scotland, this would exclude patients more likely to be living in rural communities. Therefore, in terms of efficacy of the intervention model, it is uncertain whether the model would have been less or more efficacious in these patients as it is unclear whether rurally-living patients have more or less support than their urban-dwelling counterparts. This issue could therefore not only have had an impact on the trial results but may have implications for the generalisability of this model to rural Scotland.

Secondly, by excluding patients engaged in intensive anti-cancer treatment which really only excluded those patients in the middle of a course of chemotherapy, the results of this trial cannot claim that this model is efficacious at all stages of cancer treatment. However, in practice it is unlikely that any clinician would recommend another treatment, whatever type of treatment, for a patient already engaged in intensive medical treatment for a life-threatening disease and would be more likely to wait until the course of intensive treatment had finished. Hence I consider this issue to be less important in terms of the generalisability of the sample to the target population.

For all other exclusion criteria, these criteria were imposed in order to define the target population, that is, those patients likely to benefit from the intervention. Hence psychiatric criteria excluded patients with chronic mental health problems or psychiatric comorbidity and medical criteria excluded patients with uncontrolled medical comorbidity.

In terms of patients with poor prognoses, the treatment was not designed as a treatment for cancer patients who were near death as this has the added complexity of significant physical deterioration and warrants separate research with an adapted model. The treatment in this trial was designed for relatively well outpatients with a relatively good cancer prognosis of more than a year, reflected in the fact that the majority of patients in the sample had inactive disease. The predominance of females is explained by the fact that the large lung cancer clinics were not screened as the majority of these patients would have had a poor prognosis so that the screened sample was over-representative of females and consequently of breast cancer.

A strength of the trial was that patient recruitment relied on a system of routine screening and identification of patients with MDD regardless of trial eligibility at that stage and thereby didn't rely on non-research staff to determine eligibility which can introduce selection bias with clinicians perhaps wanting to 'save' their patients from being subjected to experimental interventions thereby deeming them to be ineligible. There was some suspicion of this happening to a small degree at the start of the trial as initially we relied on the clinicians to indicate whether they thought that the patient 'would be well enough to complete a six month trial' and this

question offered an option for excluding their patient from being offered trial participation. Hence the system was changed so that there was no involvement at all by NHS staff in determining trial eligibility.

Conversely, engagement of patients by highly trained research staff may have contributed to the 'above average' acceptance rate for trials of psychological-type treatments. This may present a particular problem when considering the generalisability of not only the intervention but the whole depression management system including the initial screening of patients.

Another strength of the trial was that sampling was derived from a cancer population attending a regional cancer centre, with a catchment population of 1.5 million people in the south-east of Scotland, and is therefore fairly representative of patients attending a regional cancer outpatient department. In terms of the target population the characteristics of the sample population were in similar proportions for cancer type (mostly breast, genito-urinary and gynaecological cancers) and gender (mostly females) and with similar mean age (approximately mid 50s) to the MDD population identified in a previous study of consecutive patients attending the cancer centre (Sharpe et al 2004a).

Were the refusers different from the trial participants?

More patients with testicular, prostate or urological cancers participated in the trial, whereas more haematology patients refused trial participation, although these differences were marginal. Hence on the characteristics examined, the sample of

patients who took part in the trial was representative of the total sample of trial eligible patients diagnosed with MDD.

Recruitment of patients to this trial was challenging and although 20% of potentially eligible patients with MDD refused trial participation the strength of this study is that the commitment of the team, a vital ingredient to successful trial recruitment, resulted in a sample fairly representative of the target population and with a refuser sample not that dissimilar to the trial sample.

In summary, the sample is probably representative of adult cancer patients, without chronic or comorbid psychiatric problems and with a prognosis of good or stable health for at least 6 months and survival of at least 12 months, attending a cancer centre as an outpatient, although it does exclude head and neck and lung cancer populations.

SAMPLE SIZE

Was the sample size and outcome data available for analysis adequate to answer the research question?

The trial was powered to look for a difference of 0.21 in the mean SCL-20 scores between the groups, when it is used as a continuous scale and as the trial had originally been powered to look for a 20% difference in proportions achieving a treatment response (50% drop on the SCL-20 measure from baseline) the trial was

adequately powered for both treatment outcomes. The sample size calculations had factored in a 10% attrition rate at three months. However, very little data was lost at three months (2%) and at six months (9%) and therefore the sample size was adequate for the detection of a difference in outcome at both time points. The tight confidence intervals also suggest that the sample size was sufficient to obtain a fairly accurate estimate of the 'true' treatment effect.

ELIGIBILITY AND RANDOMISATION

Were any ineligible patients entered into the trial in error?

The two particularly difficult eligibility criteria to assess were current psychiatric problems other than the diagnosed MDD and cancer prognosis. The assessments were rigorous and where there was uncertainty about either of these two criteria, the final decision was made only after consultation with an appropriate clinician or referral to case notes (although the availability of previous psychiatric notes was limited to those patients having received care in Lothian). While it was often easier to clarify survival prognosis and indeed follow up data loss suggests that this was achieved fairly accurately, it was more difficult to detect personality disorders with the trial eligibility assessment and as a result, a small number of patients with personality disorders were entered into the trial. The frequency of this error cannot be known as this was only detected during the treatment programme for those patients who had been allocated to the additional intervention group. However, the frequency of the disorder would probably have been similar in both trial groups due to the randomisation procedure. Furthermore, the patients with personality disorders

in the trial improved, suggesting that while patients with personality disorders may have presented more of a therapeutic challenge to the nurse, their outcome was nevertheless good.

There were no particular limitations with the randomisation process. The requirement for allocation concealment was satisfied.

SPECIFICATION OF TREATMENTS GIVEN

Was the experimental intervention true to the protocol-specified model and did the treatment received as 'optimised usual care' differ between the groups?

There are potential difficulties with defining exactly the specification of treatment given. As with a cake recipe, the ingredients are defined but there will inevitably be variation in the end result because of quality differences of individual ingredients and the way in which they are mixed. Similarly, in any trial of multi-component interventions there will be a variation in the exact therapies and 'doses' given. However the components of the interventions both in the 'additional experimental intervention group' and in the 'optimised usual care group' were carefully monitored.

Firstly, the experimental intervention was delivered according to a manual, the therapists were trained, and the therapy supervised in weekly meetings. Adherence to

the treatment protocol was very strictly monitored and formally assessed, the results of which showed a very high adherence rating. The only difference between patients was the nature of the concerns worked on during sessions. The number of sessions patients received also varied although this was based on their treatment response dictated by a treatment guideline algorithm.

Secondly, analysis found that 'optimised' usual care consisted largely of visits to general practitioners and antidepressant medication with almost a quarter receiving some form of counselling. A minority of patients received specialist mental health care or alternative or complimentary therapy across both groups. Other than antidepressant use, the usual care component was similar between the treatment groups. This difference was expected, as a component of the intervention was encouragement to consult their GP about antidepressant therapy. It can therefore be assumed that the differential outcome was not the result of a significant difference in care received other than the experimental intervention.

LIMITATIONS OF THE OUTCOME MEASUREMENT

Was there any evidence of the measure not operating as intended?

For the primary outcome, symptoms were measured by self-report and although it is assumed that validity studies account for potential patient reporting bias, there is still a chance that patients may have chosen to minimise or emphasise their symptoms. This is a difficult problem to address but the assessments of patients reporting

symptom severity at either extremes of the spectrum, 'outliers', were examined and of the two outliers, (one in each treatment group), their 'extreme values' were reported consistently across self-report and interview-based assessments and over time. I am fairly certain therefore that there is no evidence to support any concern over patient reporting bias.

Anecdotally, older patients tended to under-report their symptoms or regard them as being insignificant and related more to "just old age". However, as the patients were randomly allocated to either treatment, and that the age distribution for each group was comparable, I have assumed that had this factor been operating, it would have been operating in approximately equal frequency in each group.

CLINICAL VALIDITY OF THE OUTCOME MEASURES

Does the self-rating measure mean anything clinically?

I decided that to aid the clinical interpretation of the results, a diagnostic outcome was essential rather than just the change in a numerical rating on a symptom scale and that every effort would be made to reduce the impact of observer bias (by independent re-rating of edited assessment interviews as previously discussed) and of any limitations of the measure itself (by backing it up with a clinical interpretation of the self-report symptom scale by converting it to a dichotomous outcome of treatment response or not and remission of MDD or not).

The limitations of the use of the SCID for the diagnosis of MDD in cancer patients have been previously discussed. However given these limitations and the potential limitation of poor adherence to the interview schedule and inter-rater reliability, these would presumably have applied fairly consistently across patients and to all outcome assessment points thus making the *change* in proportions of those patients diagnosed with MDD fairly accurate. This appeared to be the case as the clinical interpretation of treatment response using both interview and self rated assessments was very similar, with a difference between groups of 19% on a 50% reduction in SCL-20 score from baseline and 22% for no longer MDD on the SCID interview. Although from a purely statistical stance, too many analyses of measures of one construct are not good practice, observing convergence of the results has provided robustness and clinical validity to the findings.

BLINDNESS

Was blindness to treatment allocation achieved?

Any interview-based outcome measure has the potential to introduce bias by the interviewer becoming 'unblinded' to patient allocation. It is very difficult to achieve blindness in any intervention that involves the delivery of psychological treatments and in fact is the case in any trial that involves an intervention that looks obviously different from that offered in the control group and results in the patient knowing which intervention they are receiving.

In this trial, firstly the patients were not 'blind' to their treatment allocation. This could not be avoided by trial design and needs some consideration of the effect this could have had on the results. Inevitably some patients would have had some preference for one of the two treatments over the other. This could have resulted in patients feeling disappointed by not receiving their preferred choice of treatment and as a result they may have consciously or unconsciously exaggerated or minimised their trial outcome assessment responses. There is however no recognised way of measuring or preventing this bias and furthermore no way of assessing the potential impact of this on the results as not all patients would have considered (and indeed didn't) the additional nurse-delivered intervention as the desirable or preferred treatment option. Therefore it is not clear whether the resulting effect would have inflated the treatment effect. If one hypothesised that the additional intervention was the preferred option and that patients receiving this minimised their symptoms at their outcome assessments and that those allocated to usual care maximised their responses then the overall effect may have resulted in a treatment effect inflated beyond the 'true' treatment effect. In conclusion, response bias in this trial could not be proactively prevented nor accounted for in any way in the analysis and it remains therefore that response bias could have operated in this trial.

NON-SPECIFIC TREATMENT EFFECTS

Was the comparison group appropriate?

An important factor in this trial or in any trial of psychological treatment versus no psychological treatment is whether merely an equivalent amount of 'attention', that is the presence of the therapist for a similar period, in this case approximately seven sessions, could have had a similar therapeutic effect on the patient. So in other words a stricter comparison of usual care plus the additional nurse-delivered intervention versus usual care plus speaking with a nurse about non-health related or 'neutral' topics may methodologically have been more correct. However practically this would have been difficult to do in terms of controlling the topic of conversation. Furthermore the literature on the treatment of MDD suggests that it is unlikely that only 'attention' would be effective. There is therefore no way of knowing from this trial design to what degree non-specific treatment effects in the intervention group, if any, were operating.

ACTIVE INGREDIENT

What was the most 'effective' ingredient in the model?

The trial was not designed to identify the active or most effective 'ingredient' nor to determine whether a simpler intervention would have been as efficacious. Previously conducted studies have tested various components of this model in isolation, the results of which have been previously discussed. However, I did conduct exploratory

analyses to establish whether improving coping skills mediated clinical improvement, the results of which suggested that increasing patients' confidence was associated with clinical improvement. It does not establish a causal relationship and cannot establish which component of the model was the *most* 'effective' ingredient, merely that an ingredient of the PST component contributed in some way to the overall efficacy of the intervention.

MAINTENANCE OF TREATMENT EFFECT

Does the treatment effect last beyond the intervention period?

Whether the treatment effect is sustained beyond six months has not been established. Follow up is on-going and will be reported when data are available but the trial is not designed or funded to explore longer-term effects. However, a recent systematic review (Gilbody et al 2006) suggests that the treatment effect of collaborative care models extends beyond a year with effects still evident at 5 years, although collecting data to show this in cancer populations would be a challenge because of loss of data due to death.

COMMENT

In summary, the trial had methodological limitations. The major unavoidable ones were: the possibility of measurement bias, that is the effect of patients being aware of which treatment they were receiving; response bias, that is the effect of patients

exaggerating or minimising their trial outcome assessment responses; and the possibility that non-specific treatment effects may have been operating, the implications of which, if any, are impossible to determine. However, a large treatment effect was observed on the primary outcome measure with statistically significant benefits seen on all other measures other than physical functioning suggesting that the interpretation of the findings is fairly accurate.

So although non-specific treatment effects and measurement and response bias could not be avoided, the trial had the advantages of recruitment via mass screening of patients rather than referral, rigorous patients selection, a sample population of mixed cancers at different stages of disease and treatment, known confounders accounted for by using minimisation in randomising patients, the use of a strict quality assurance procedure, the use of more than one therapist and very few missing data, making the findings robust.

CHAPTER 10: OTHER RELEVANT RESEARCH

Sections

Trials published before the start of this trial

Trials published after the start of this trial

The Pathways Study

The Latina Study

List of Tables

Table 10.1: Key trials of the collaborative depression care model

List of Figures

Figure 10.1: The development of the collaborative depression care model

TRIALS PUBLISHED BEFORE THE START OF THIS TRIAL

Prior to starting this trial, there had been no published trials of multi-component interventions for the management of MDD in cancer patients or patients with chronic illness. However there were published results of the three main early efficacy trials of models of collaborative care models of MDD management in primary care settings (Katon et al 1995, 1996 and 1999). The first of these trials used a simplified model with a patient education component, the second trial added a brief problem solving treatment to the package and the third trial used a stepped care model whereby patients not responding to standard conventional treatment would receive enhanced care of a similar package to that used in the 1996 trial. Following this, two effectiveness trials of the simplified collaborative care model (Rost et al 2001) and the additional PST model (Wells et al 2000) were published. A number of other trials were conducted extending the model to different patient populations of high utilisers of medical care (Katzelnick et al 2000), older people (Unutzer et al 2002) and low-income women (Araya et al 2003) and extending its mode of delivery to phone-delivered treatment (Hunkeler et al 2000), detailed in Table 10.1. The development of the collaborative model, with key trials, are depicted in Figure 10.1.

TRIALS PUBLISHED AFTER THE START OF THIS TRIAL

Since the start of the trial, a second efficacy trial of a phone-delivered collaborative care model for MDD in primary care has been published (Simon et al 2004). However publications of collaborative care models for the management of MDD applied to chronic illness or cancer have been few. Katon and colleagues (2004)

published findings from their trial of extending the stepped care model to a population of patients with diabetes. This was the first reported trial of this model applied to chronic illness. Of key relevance to my research however has been the publication of a randomised pilot study of the model applied to cancer patients by the group in Los Angeles (Dwight-Johnson et al 2005). These two trials will be discussed in more detail below:

The Pathways study (Katon et al 2004)

This was a randomised efficacy trial comparing the stepped care collaborative model of depression management in patients with diabetes with usual depression management in terms of outcomes in depression and diabetes. A total of 329 patients were recruited from nine primary health care centres in one health care system with diabetes mellitus and comorbid persistent depression and/or dysthymia as identified by self-report measures. Unlike the trial described in this thesis there was no interviewed based verification of the self-report 'diagnosis' and the depression severity scale score for trial entry was set much lower (at 1.1) than that used in this trial. The sample in fact comprised 70% dysthymia and less severe depression and was therefore quite different from the sample in this trial in terms of severity and chronicity.

The experimental treatment delivered was enhanced education and support of antidepressant medication prescribed by the GP or PST provided by a supervised depression clinical nurse specialist in collaboration with the GP over twelve weeks in approximately half hour sessions spaced at two weekly intervals with continued

monitoring for up to a year. Treatment was provided in a stepped fashion whereby patients received different types and intensities of services if they still had persistent depressive symptoms at twelve weeks. Their treatment programme is therefore more focussed on non-responders than this trial, targeting those with no treatment response by a set period more intensively and actively engaging them in further treatment, although in content very similar to my intervention and delivered by a nurse. However it is unclear whether they too used nurses without any prior mental health training.

The pre-specified criteria for good outcome, defined as 'response to treatment', was the difference between the treatment groups in proportions achieving firstly a forty percent reduction from baseline and secondly a fifty percent reduction from baseline in the SLC-90 depression scale score at six and twelve months. An analysis of group trends over time in mean depression scores was also performed. Outcomes expressed as treatment response found a statistically significant and clinically important but small difference between the groups in proportions achieving a 40% reduction in depression scores at twelve months but not at six months and no statistically significant differences at either time points between groups when a more stringent clinical indicator of 50% reduction was applied. Outcomes expressed as change in mean depression scores over time found a statistically significant difference between the intervention groups at six and twelve months. These results are not consistent with mine. The only clinically defined outcome that was statistically significant was for a 40% reduction in depression scores and only at twelve months. The standardised effect size of the results was 0.11. Although I do not have twelve month

data from this trial for direct comparison, my six month data on a 50% reduction in SCL-20 score from baseline as a standardised effect size of 0.22, is a bigger effect size than that found in the Pathways Trial.

A similar comparison can be made however with the care received in the usual care group in that usual care was actually 'enhanced usual care', enhanced by encouraging the patient to discuss their depression with their GP and that a significant number of the usual care patients received antidepressant medication.

In summary, the patient population was similar in terms of comorbid chronic illness but not comparable in terms of depression severity. The treatment, although similar in content, was delivered by a supervised nurse but the treatment programme was longer and intensified for 'non-responders'. The outcome measure was the same but treatment response was defined at a lower cut-off. However, overall, the Pathways trial was the first trial of a collaborative model applied to chronic illness. The finding of a delayed larger treatment effect is comparable in part with the results of my trial where the treatment effect has increased over time.

The Latina study (Dwight-Johnson et al 2005)

This was a randomised pilot trial comparing the collaborative care model of depression management in patients with cancer in an Oncology setting with usual depression management in terms of depression outcomes and cancer treatment adherence. Fifty-five female low-income Latina patients (with MDD, persistent depressive symptoms for a month or dysthymia as assessed by self-report measures

rather than interview-based diagnoses) were recruited from the breast and gynaecological outpatient clinics of a US public sector Oncology centre. Although there was no trial entry criterion for depression severity, the mean PHQ-9 score at baseline was greater than 10 and the exclusion criteria applied were the same as those used in my trial and patients were screened as opposed to recruited by referral, hence capturing a sample representative of fairly well cancer patients with no significant psychiatric comorbidity other than the depression. However, the patient sample is not directly comparable with my trial sample in terms of depression severity and chronicity, ethnicity, social deprivation status and is gender-specific. However, this is first trial, albeit a pilot study, from another research group that has investigated the efficacy of the collaborative care model for depression in a cancer population and is therefore the only comparison that can be made to date.

The experimental treatment delivered in the Latina trial was either eight weekly sessions of PST provided by a psychiatrist-supervised depression clinical specialist (social worker) or antidepressant medication (prescribed by the Oncologist and monitored by the depression specialist) as their first-line treatment, plus education and support to increase antidepressant medication adherence and access to appropriate services. Patients not responding to treatment at the end of eight sessions of PST or by week eight, as defined by not achieving a 50% reduction in depressive symptoms, were reassessed by the psychiatrist and treatment adjusted.

Their treatment programme is very similar to the one used in this trial. The treatment provider although not a nurse was supervised by a psychiatrist and received regular

scheduled supervision meetings. The treatment programme was delivered according to a manual, depressive symptoms monitored and treatment adjusted according to treatment response using the same clinical indicator of response as in my trial. The differences appear to be primarily to do with the package of treatment offered. It is not clear whether patients had the option of PST together with antidepressant medication. If not, then this is a major difference from the model in my trial, where the treatment package consisted of multiple components including antidepressant medication and PST although the combination of these two components was not compulsory. The usual care component was also similar to that provided in my trial with the diagnosis being given to the doctor or main health care provider and documented in the patient's Oncology notes.

The pre-specified criteria for good depression and cancer treatment adherence outcomes was the difference between the treatment groups in proportions achieving 'response to treatment', defined as a fifty percent reduction from baseline in the PHQ-9 depression scale score at eight months, and the proportions adherent to cancer treatment. Statistically significant differences between groups were found in depression outcome but not for cancer treatment adherence. These results although only preliminary and imprecise, as indicated by the wide confidence intervals, are consistent with mine. Furthermore, non significant findings for effect on physical functioning are also consistent. From their discussion of barriers to implementing this model in the Oncology setting, problems with securing additional consultation slots with the Oncologist in order to prescribe an antidepressant were mentioned. Integration with the Oncology setting has been an on-going and evolving component

of my model and consistent with the Latina study conclusion, it seems necessary to provide additional resources for the implementation of the model rather than using existing resources.

In summary, the patient population was similar in terms of comorbid cancer but again not comparable in terms of depression severity. The treatment although similar in individual components was different in the package offered to patients. However, overall, the Latina trial was the first trial of a collaborative model applied to cancer conducted by another research group.

In addition to these two trials, three systematic reviews of depression management programmes published after the start of my trial (Badmagarav et al 2003; Neumeyer-Gromen et al 2004; Gilbody et al 2006) have confirmed the efficacy and effectiveness of primary care based multicomponent interventions for the treatment of depression. Although not time-equivalent, comparing the treatment effect size of 0.43 (95% CI 0.15 to 0.72) from this trial's three month outcome results with the six month outcome pooled effect size of 0.25 (95% CI 0.18 to 0.32) from the most recent systematic review (Gilbody et al 2006), illustrates that the results of this trial are similar in effect.

On a cautionary note however is that although there is sufficient evidence now to demonstrate a reliable, consistent and statistically significant benefit of the collaborative model over usual care for depression in primary care, it should not be assumed that this model can be applied to other disease-specific patient populations

without further research. A Canadian study of case management by nurses in patients with heart disease found no overall impact on either survival or psychological outcomes in post-myocardial infarction patients with high levels of distress and even showed increased cardiac and all-cause mortality in women who received the intervention (Frasure-Smith et al 1997). However the patient sample was not of identified cases of depression but rather patients with high levels of distress, the nurses had not received any training in psychiatric disorder screening or psychotherapeutic techniques and case management did not involve any direct intervention other than reassurance, advice and referral. Hence although the model could not be considered 'true' to the collaborative care model, it does illustrate that this type of care may not in fact be beneficial to all groups of patients.

An interesting finding in my trial was the lack of effect of the intervention on physical functioning. This was not an unexpected finding, and is consistent with those of other trials and the review by Badmagarav et al (2003) that found very little evidence of effectiveness of disease management programmes for depression on physical functioning with the pooled estimate showing an effect close to that of usual care. Furthermore, aiming to achieve any benefit in physical functioning may be unrealistic in patients with chronic illness, especially illnesses like cancer that have a natural course of physical deterioration.

In summary there is insufficient evidence to draw strong conclusions about the efficacy and none about the effectiveness of the collaborative care model for the

management of MDD in cancer patients. However, this trial provides the first piece of robust evidence of its efficacy in a relatively well cancer population.

Table 10.1: Key trials of the collaborative depression care model

Authors & year of publication (country)	Setting (sample size)	Intervention package	Control group	Nurse involvement y/n	Outcome measure	Results
Katon et al 1995 (USA)	Primary care (n=127 of which MDD=91)	GP education + monthly case conference + enhanced consultations (2xGP visits + 2xpsychiatrist visit) + patient education (video + written) + scheduled follow-up.	Usual care	N	50% reduction in SCL-20	For MDD subset only: 74% vs 43.8%
Katon et al 1996 (USA)	Primary care (n=153 of which MDD=65)	As above + Problem-solving therapy delivered by psychologist	Usual care	N	50% reduction in SCL-20 (primary outcome at 4 months)	For MDD subset only: 70.4% vs 42.3%
Katon et al 1999 (USA)	Primary care (N= 228 persistent MDD i.e. not responding to 8 weeks of usual care)	Stepped care model: patient education + 2 visits to psychiatrist in primary care + ongoing management advice to patient and GP + case management by nurse	Usual care	Y	Mean SCL-20 scores and MDD diagnosis at 3 and 6 months	Significant effect over time on SCL-20 and 40% vs. 23% at 3 months and 44% vs. 31% at 6 months no longer MDD diagnosis
Hunkeler et al 2000 (USA)	Primary care 3-arm trial (N=302 MDD or dysthymia patients starting	Nurse telehealthcare: augmentation of usual SSRI	Usual antidepressant care	Y	50% reduction in Hamilton Depression Rating Scale (HAM-D) at	Nurse telehealthcare vs. usual care = 50% vs. 38% at 6

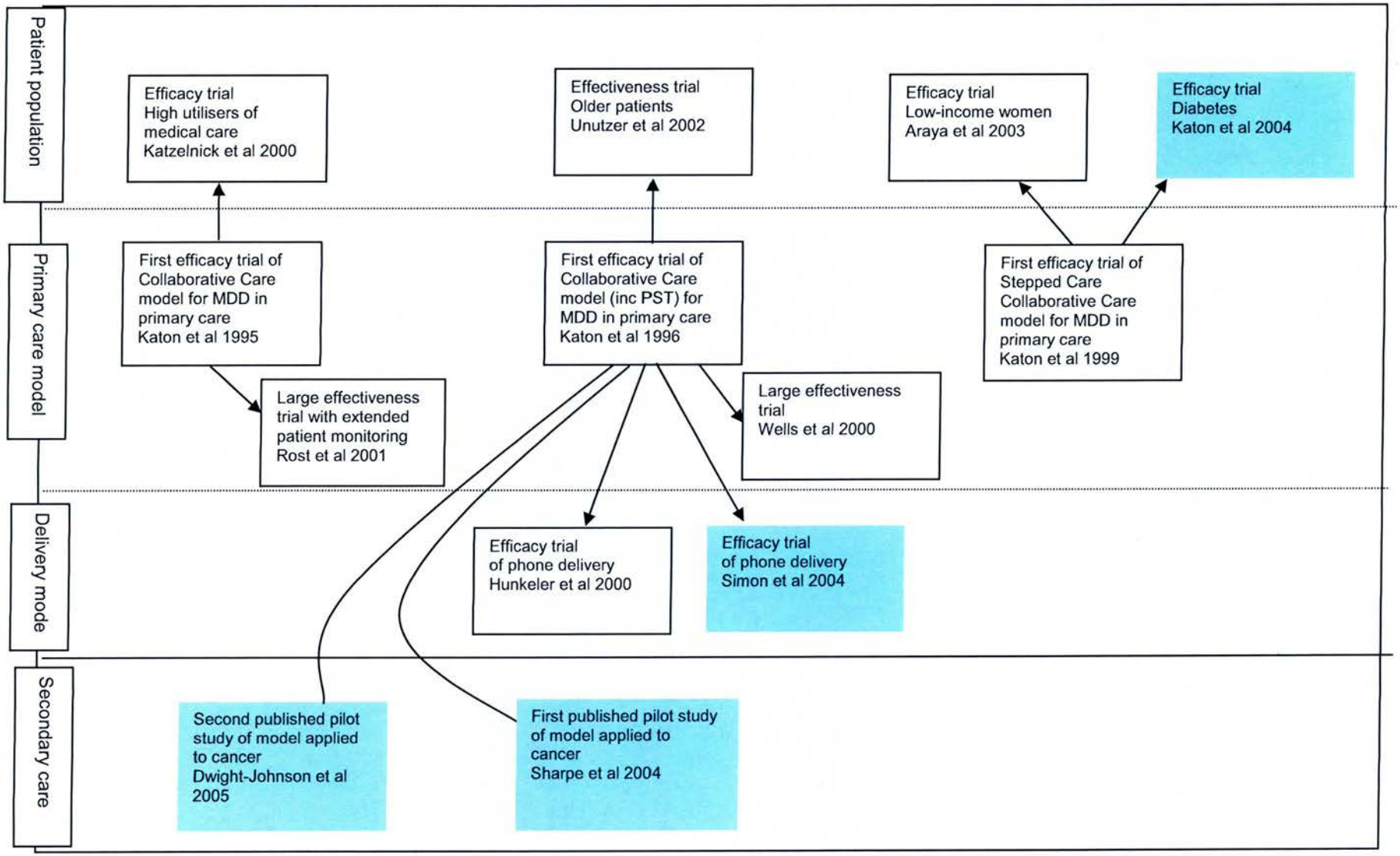
	SSRI antidepressant therapy)	medication. Phone-delivered nurse case management (12-14 weekly 10 min calls over 16 weeks) consisting patient education, support (problem-solving and activity scheduling) and treatment monitoring to algorithm vs. peer support plus above vs. usual care			6 weeks and 6 months	weeks and 57% vs. 38% at 6 months but didn't alter medication adherence
Katzelnick et al 2000 (USA)	Primary care (N=163 practices with 407 high medical care utilising patients with MDD or MDD in partial remission)	Depression management programme (DMP): GP education + Antidepressant prescribing guidelines, patient education, and case management by primary care mental health workers	Usual care	N primary care mental health workers (GPs, psychiatrists and postgraduates with mental health experience)	50% reduction in Hamilton Depression Rating Scale (HAM-D) at 12 months	53.2% vs. 32.8% and HAM-D scores better by 9.2 points vs. 5.6 points

Wells et al 2000 (USA)	Primary care 3-arm trial (N=46 practices with 1356 patients)	Dissemination of DMP: nurse case management (pt education plus behavioural activation) plus either a) encouragement to receive 12 – 16 sessions of CBT provided by local psychotherapists or b) antidepressant medication	Usual care	Y	no longer meeting criteria for MDD on CES-D (Centre for Epidemiologic Studies Depression Scale) at 6 months	60.1% (2 intervention arms combined) vs. 50.1%
Sherbourne et al 2001 (USA)	Follow-up report of Wells et al 2000 trial	As above	As above	Y	As above	58.4% vs. 48.8% at 12 months
Rost et al 2001 Follow-up report 2002 (USA)	Primary care (N= 12 practices with 479 patients) 2002 paper N=211	QuEST: patient education + support + treatment monitoring to algorithm over 7 months by nurses *Then* Follow-up 2002 paper: practice nurse-delivered on-going care (management over phone) from 7-24 months	Usual care	Y (non-psychiatric trained nurses)	Modified CES-D (Centre for Epidemiologic Studies Depression Scale) at 6 months	Improved depression scores by 8.2 points (95% CI 0.2-16.1) 2002 paper: Increased remission rates by 33% (95% CI 7 to 46%)

Katon et al 2001 (USA)	Primary care relapse prevention trial (N=386 recurrent MDD or dysthymia post 8 week course of antidepressants)	relapse prevention plan + 2 in-person and 3 phone consultations with depression specialist over 1 year period	Usual care	Y (either nurse, psychologist or social worker)	At 3, 6, 9 and 12 months	Intervention patients had an average score of 0.8 less over time symptoms but no difference in relapse rates between groups
Unutzer et al 2002 (USA) Follow-up report by Hunkeler et al 2006	Primary care (N= 18 practices with 1801 older patients with significant co-morbidity)	IMPACT: (Improving mood: promoting access to collaborative treatment): 20-min educational videotape and booklet + care manager (nurse or psychologist) + choice of antidepressants and/or PST + active FU monitoring with PHQ-9	Usual care	Y (either nurse or psychologist)	Mean SCL-20 scores and 50% reduction in scores at 3, 6 and 12 months	Difference in means of 0.4 in favour of intervention and for 50% reduction, 45% vs19% at 12 months Long-term outcome of IMPACT trial at 2 years: difference in SCL-20 scores of 0.23.
Araya et al 2003 (Chile)	Primary care (N=240 low-income female patients aged 30-60)	Stepped care multi-component intervention: 7 sessions (plus 2 booster sessions) group pt education + structured treatment monitoring plus for those not responding to treatment at 6	Usual care	Y (either nurse or social worker)	Hamilton Depression Rating Scale (HAM-D) response of <8 at 3 and 6 months	Adjusted difference in means = -8.89 (95% CI -11.15 to -6.76) at 3 months and response of <8 at 6 months = 70% vs. 30%

		weeks, Antidepressants plus Ad monitoring by social worker or nurse				
Katon et al 2004 (USA)	Primary care (N=329 diabetic patients with MDD and dysthymia, mostly 70% dysthymia)	Pathways stepped care model: nurse case management + patient antidepressant education and support and/or PST	Usual care	Y	40% and 50% reductions in mean SCL-20 score at 6 and 12 months	Improved depression outcome at 12 months but not 6
Simon et al 2004 (USA)	Primary care 3-arm trial (N= 600 patients starting antidepressant medication)	Tele-healthcare management Vs Tele-healthcare management + 8 phone-delivered CBT sessions	Usual care	N (care managers were mental health clinicians)	Mean SCL-20 scores over time (6 weeks, 3 and 6 months) and 50% reduction in scores at 6 months	Thcm + CBT vs. usual care = lower mean SCL-20 and at 6 months was 58% vs. 43% on 50% reduction
Dwight-Johnson et al 2005 (USA)	Pilot RCT Oncology setting (N= 55 low income Latino female cancer patients)	Antidepressants + case review + 8 sessions PST	Usual care	N (social workers)	50% reduction in PHQ-9 at 4 and 8 months	At 8 months = OR=4.51 (95% CI 1.07 to 18.93)

Figure 10.1: The development of the collaborative depression care model



CHAPTER 11: IMPLICATIONS OF FINDINGS

Sections

The Trial
    Clinical implications
    Implications for Research

Long-term outcome

Predictors of outcome
    Clinical implications
    Implications for Research

Comment

Clinical Implications

The trial reported here has several clinical implications:

1. An efficacious and potential effective intervention has been developed for patients with MDD comorbid with cancer
2. Adding the intervention to usual care achieves a better outcome than usual care alone
3. The number of previous episodes of depression, length of current episode of depression, depression severity and possibly extent of cancer disease may be independent predictors of outcome
4. There is suggestive evidence that increasing patients' confidence in their ability to control an episode of depression is associated with good outcome

Firstly, it would be premature to recommend this intervention for general clinical practice. The evidence is only preliminary and it is likely that the treatment effect will be diluted when transferred into routine practice. For instance, in this type of intervention trial the clinicians' and therapists' abilities are likely to have an impact on the patient's recovery more so than a clinician's impact in a drug trial. Caution is therefore needed when introducing such a treatment into practice because it is effectively generalising the achievement of the most skilled and experienced clinicians and nurses and hence requires testing in a large pragmatic trial to provide evidence of its generalisability and effectiveness.

Secondly, providing this intervention in the UK NHS may require additional resources. It is not clear whether existing clinical cancer nurse specialists would take

on the role of depression management or whether a new 'breed' of clinical nurse specialists would deliver this intervention. Whatever clinical configuration evolves will depend on both the results of the next planned effectiveness trial and the way in which the NHS is prepared to deliver the model.

Implications for research

Measures

Although primary care trials to date have been fairly consistent in their use of measures for the initial diagnosis and for assessment or outcome, there has been considerable debate about the diagnosis of MDD in cancer patients. However, as more trials are undertaken, the need for uniformity is essential in order to compare findings. Further validation studies in cancer populations are required for the main measures that have been used previously in the primary care trials, that is the SCL-20, the HAM-D, the CES-D, the DSM1V SCID interview criteria, the PHQ-9 and maybe more radically the single-item screener, "Are you depressed most of the time?"

Methods

The efficacy of the collaborative depression care model for minor depression has not been proven. Early studies failed to show any significant benefit for this group of patients (Katon et al 1995 and 1996). Future research with this model in cancer patients should also therefore focus on more severe depression, providing an opportunity to develop an appropriate intervention for forms of lesser distress.

The efficacy of the collaborative depression care model has also not been applied to cancer population subgroups such as poor prognosis patients. As previously mentioned this may require adaptation of the model necessitating piloting before an efficacy trial can be undertaken.

More research is also necessary to test the model in other chronic illnesses and its effect on medical outcome. This has already begun with Katon's trial in patients with diabetes (Katon et al 2004).

Finally, given that there is evidence to suggest that the coexistence of cancer and depression is associated with an increased risk of death from all causes (Onitilo et al 2006), another area of research interest would be the effect of depression and its management on survival. This would be methodologically challenging in a population with high death rates at varying intervals although perhaps more feasible in cancer-specific populations with fairly accurate predictions of survival.

LONG-TERM OUTCOME

Indications are that there is long-term benefit from primary care based collaborative depression care models (Gilbody et al 2006). The research challenge is therefore to provide long-term outcome data for a cancer population. However the nature of the disease is such that data loss from deaths may preclude any such analyses.

PREDICTORS OF OUTCOME

Clinical Implications

It may be clinically more logical to apply a stepped approach to the management of those patients with a previous history of depression, with severe MDD and those with more advanced disease as these may be predictive of poor outcome. Thus additional treatment or appropriate referral could be made if a treatment response was not achieved within a set period as done in other trials. However, I suspect that for patients with advanced disease, the model may require adaptation to accommodate deteriorating physical functioning and reliance on others for help, thus compromising the essence of the model, that of control over one's illness.

Implications for research

The identification of independent predictors of poor outcome provides information for future trials, having implications for both the randomisation of patients and the analysis of the data. It is now clear that depression history, current severity of depressive symptoms and extent of the cancer are possibly the more important factors in achieving comparable groups than gender, age and cancer type.

COMMENT

However, in spite of emerging evidence for an effective approach to the management of depression in cancer patients, there remains a fundamental question: *Do the patients want the treatment and will the health care team give it?* From my

experience of this trial, I think there may be a barrier to be overcome, before depression management can ever be accepted into routine practice, that is, a fundamental belief underlying the all too often heard comment of "Well, it's understandable they have depression, after all they have cancer!"

In my view, the key issue is not about whether depression is an understandable reaction or not but is about whether it is treatable or not? The results presented in this thesis provide evidence for the fact that severe depression in cancer *can* be treated so returning to the question of whether it is understandable or not makes the question rather pointless and the lack of treatment possibly unethical.

CHAPTER 12:
THE CURRENT STATUS OF THE COLLABORATIVE CARE MODEL APPROACH TO THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN CANCER PATIENTS

There have been no reported studies to date of the efficacy of a nurse-delivered multi-component intervention for the management of MDD in cancer patients. There is now sufficient evidence to prove the effectiveness of collaborative depression care models in primary care and preliminary evidence for its efficacy in patients with comorbid chronic illness. The trial reported here is, as far as I am aware, the first randomised controlled trial of collaborative care that has been extended beyond depression managed in primary care to depression managed in secondary care integrated with primary care thus providing a fourth element of oncology care to the three elements of chronic disease management of: case manager; a primary care physician; and access to specialist mental health care. Furthermore, the trial is the first trial of a collaborative model outside of the US and the first in cancer.

There is however growing evidence of the efficacy of nurse-delivered interventions for symptoms other than depression in cancer populations. Of the few reported evaluations of nurse-delivered interventions in cancer patients, favourable outcomes were shown in two large randomised controlled trials: the management of distress associated with breathlessness in lung cancer patients (Bredin et al 1999); and an intervention designed to reduce symptom limitation for patients undergoing chemotherapy (Given et al 2004).

CONCLUSIONS

Chapter 13: Review of Aims and Hypotheses

Chapter 14: Future Research

CHAPTER 13: REVIEW OF AIMS AND HYPOTHESES

Sections

Aims and hypotheses

Testing the intervention

The overall aim was to improve the management of depression in patients with cancer. The specific objective was to:

1. **Test the efficacy of this intervention model for the treatment of MDD in cancer patients of mixed diagnoses in a randomised controlled trial by comparing usual care with usual care plus the nurse-delivered, psychiatrist-supervised multi-component intervention by:**

    a. **Measuring the primary outcome of trial participants at 3 and 6 months**

The efficacy of the intervention model was tested at three months using the primary outcome measure of the SCL-20. A substantially better and statistically significantly better outcome was obtained for those patients receiving the additional intervention with the benefit being sustained at the six-month follow-up. The main hypothesis that usual care plus a nurse-delivered, psychiatrist-supervised multi-component treatment intervention would reduce symptoms of major depressive disorder in patients with cancer to a greater extent than usual care alone was supported.

    b. **Measuring other outcomes at 3 and 6 months, specifically:**

i. clinically relevant response to treatment and remission of depressive symptoms

The efficacy of the intervention model was tested at three months using clinically important criteria of treatment response and remission. There was a statistically

significant difference in proportions of patients achieving the pre-specified secondary outcomes between the groups at three months. Observing convergence of the results has provided robustness and clinical validity to the findings of the primary outcome. Furthermore, the findings suggest that the differences in benefit may even be larger at six months. The hypothesis is shown to be supported that at the 6 month follow-up, patients treated with the additional nurse-delivered intervention will maintain the benefit and have benefit superior to those patients who were allocated to usual care only.

ii. anxiety, physical functioning, coping, problem solving ability and satisfaction with treatment

The efficacy of the intervention model was tested at three months using measures of anxiety, physical functioning, coping and problem-solving. A greater reduction in anxiety and a greater increase in all coping measures were observed in the intervention group. However, no significant differences were observed on the measure of physical functioning between treatment groups at three months. This was not a surprising finding and reinforces findings of similar trials in chronic illness. Although no formal significance testing was performed at six months, the treatment effect for physical functioning was larger in favour of the intervention group.

Satisfaction with treatment measured at six months found that the satisfaction of patients receiving the intervention was greater than those receiving usual care.

iii. the association between improvement in depression scores and aspects of confidence, coping and support

The associations between improvement in depression scores and measures of confidence, coping and support were explored at three months. A correlation was found between improvement in depression outcome and change in measures of confidence but not of support and coping, suggesting that increasing patients' confidence may have had an influence on outcome. The hypothesis that the additional nurse intervention improves outcome by a) increasing the patient's confidence to cope with concerns and b) increasing their coping skills by teaching them a skill to tackle their concerns and c) increasing their access to and use of social support therefore receives some support and can only be considered as exploratory findings.

iv. the extent to which baseline factors predict a good outcome at 3 months (although this was exploratory and not part of the pre-specified statistical analysis plan)

At the 3 month outcome, exploratory analysis suggested that the principal independent predictors of good outcome were: allocation to the additional intervention arm; no previous history of depression; a current episode of less than one year's duration; and a low baseline depression severity score. It was surprising that neither gender, nor any cancer related variables such as extent of disease nor whether the patient was receiving active anti-cancer treatment emerged as predictors of response.

In conclusion the overall aim which was to improve the management of depression in cancer has been largely achieved. However, a large effectiveness trial is now required to determine whether the intervention is effective when implemented out-with a research environment in the 'real world' of a health care system.

CHAPTER 14: FUTURE RESEARCH

Sections

The evaluations of interventions

Comment

There is now sufficient evidence of the efficacy and effectiveness in primary care of the collaborative depression care model (Gilbody et al 2006).

Further research is now required to evaluate the application of this approach to other patient populations such as those with comorbid medical disease.

THE EVALUATION OF INTERVENTIONS

This is the first reported efficacy trial of a collaborative care model for MDD in cancer patients. Hence it requires both replication and evaluation of effectiveness. Since the completion of this research, further funding has been secured to conduct a large pragmatic trial across Scotland to investigate the effectiveness of this approach to depression care for cancer patients. A proof of concept trial of this model applied to patients with poor prognosis has also received funding and will be conducted in Edinburgh.

There are three issues that warrant some thought before further research is undertaken:

Firstly, Gilbody's review (Gilbody et al 2006) indicated that the addition of psychotherapy to medication was not associated with increased effect size suggesting that psychotherapy may not be an 'effective' ingredient of treatment. Future research into the intervention proposed here should therefore assess the benefit of the problem solving therapy. Perhaps a model that provides support and monitoring to ensure

patient compliance to antidepressant medication would be as effective and less costly to provide.

Secondly, trials using case managers with a mental health background found greater efficacy (Gilbody et al 2006). However it remains unclear whether it is better for the case managers treating depression in cancer patients to have a mental health background or a cancer background.

Thirdly, there is a need for trials large enough to be able to identify predictors of response. Exploratory findings from this research suggest that the severity and length of the current depressive episode and a previous history of depression predicts response to treatment. This may therefore provide some substance on which to base a refined model, for instance a model whereby patients at risk of poor response to treatment are given more intense treatment or are provided with an additional component.

COMMENT

In summary, there is a robust body of evidence to support the effectiveness of collaborative depression care in primary care but only limited evidence of its efficacy and effectiveness in patients with comorbid medical conditions and next to none in cancer patients. There is therefore a pressing need for research into the management of depression in patients with cancer.

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APPENDICES

Appendix A: Treatment Manual

TREATMENT OF MAJOR DEPRESSIVE DISORDER IN ONCOLOGY PATIENTS

Nurse treatment manual

Vanessa Strong, Michael Sharpe, Ann Cull,
with advice from Peter Maguire, Amanda Ramirez, Allan House,
Wayne Katon, Arthur Nezu, Christine Nezu and Iona Davis

REQUIREMENTS

This manual presupposes that the treating nurse has:

1. Good knowledge of oncology nursing
2. Attended formal training in

- Interviewing and eliciting concerns
- Diagnosing and assessing depression and suicide risk
- Use of antidepressant medication
- Advanced Coping Skills Training therapy

It is intended to be administered only after demonstration of competence and under the supervision of a qualified mental health professional. This manual is a framework for delivering the treatment and the nurse requires expertise to tailor this treatment to the individual patient. Text in *italics* are recommendations for presentation of facts and/or ways of questioning.

OUTLINE OF TREATMENT

The treatment is based on a detailed assessment of the patient and is carried out in 6 sessions with the possibility of extending the therapy to a maximum of 10 sessions over a maximum of 13 weeks. Sessions 1 and 2 are to be completed in the first week – subsequent sessions are spaced at approximately weekly intervals.

GENERAL POINTS

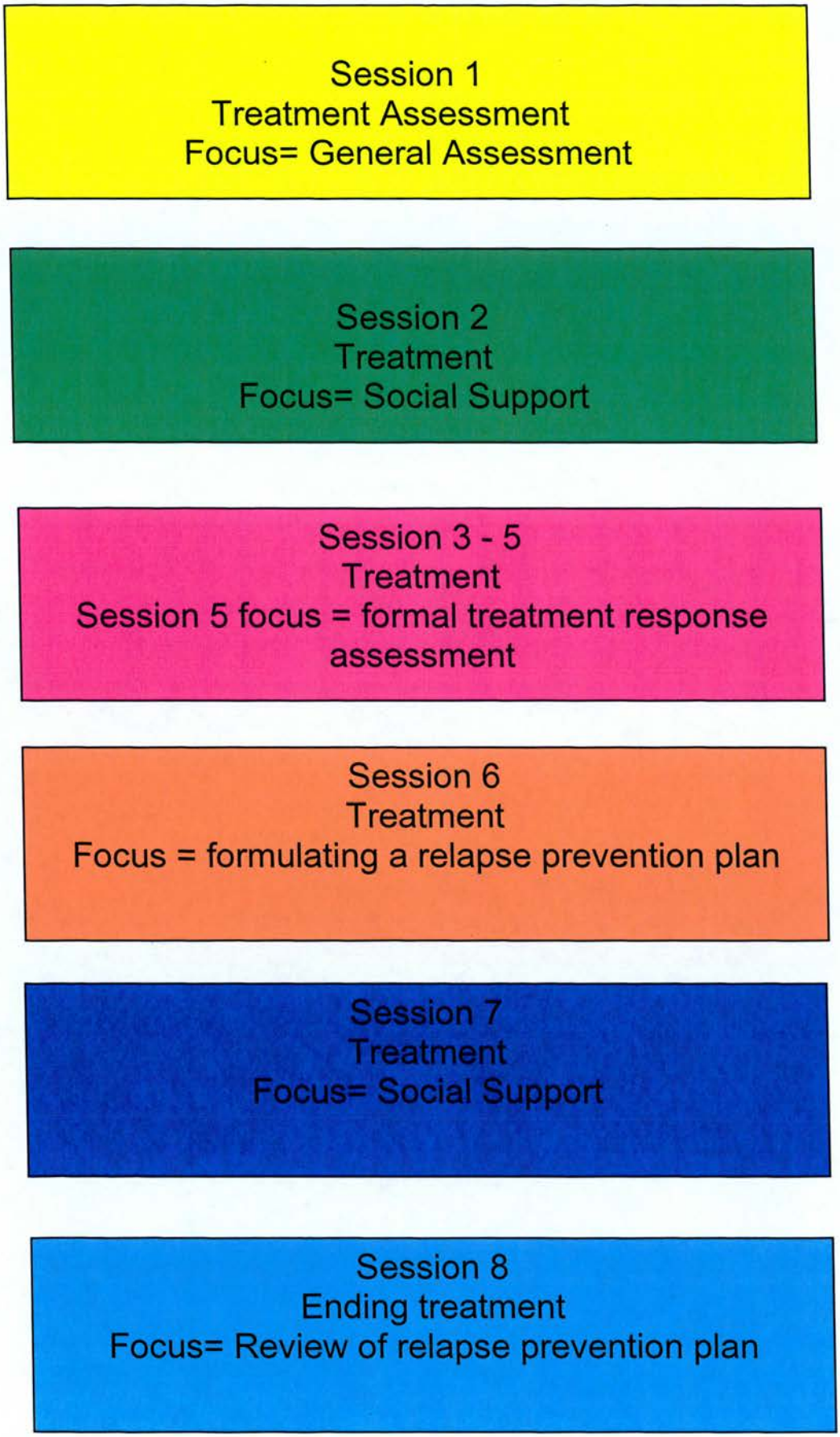
Interpersonal style

- BE POSITIVE - 'well done'
- BE EMPATHIC – 'that must have been hard for you'
- BE CURIOUS – 'what was that like; how do you feel about that?'
- BE SPECIFIC – 'tell me exactly what that is like' ' can you give me an example?'
- BE PRACTICAL - 'let's see just how that would work'
- BE FACILITATING – 'would you like to try that out here first?'
- BE REALISTIC- 'is that goal something we can reach - or should we rethink it?'

RECORDING TIME / COST OF TREATMENT

For each patient, record:

- all contact time (face to face and on phone)
- time spent in administrative duties
- time psychiatrist/psychologist gives nurse in supervision
- Any face to face time between psychiatrist /psychologist and patient
- whether another person (and relationship) has accompanied the patient to the session.


Session 1
Treatment Assessment
Focus= General Assessment
Session 2
Treatment
Focus= Social Support
Session 3 - 5
Treatment
Session 5 focus = formal treatment response assessment
Session 6
Treatment
Focus = formulating a relapse prevention plan
Session 7
Treatment
Focus= Social Support
Session 8
Ending treatment
Focus= Review of relapse prevention plan

Session 1 Treatment Assessment
Focus= General Assessment

AIMS:	Explain approach and length of treatment (start planning for end of therapy) Engage patient Elicit exhaustive list of concerns Elicit patient's understanding of their cancer and depression Assess depressive symptoms and suicide risk Find out what treatment they have had and are receiving now Clarify other problems Obtain background history and current circumstances/resources Explain the approach of advanced coping skills training Mini coping technique example using depression as the problem Agree approach and plan treatment Patient action re antidepressants
DURATION:	1 to 1.5 hours
OUTPUTS:	List of concerns Patient's perception of cancer and depression Depressive symptoms on SCID and suicidality Initial concerns list Initial plan re: depression
HOMEWORK PATIENT:	Read patient information booklet See GP re: antidepressants or appropriate homework task
HOMEWORK NURSE:	Letter to GP re: patient and antidepressants (faxed/sent/phoned) Letter to patient's Oncologist (with copies to any other health care professionals involved) with GP copy letter Discuss in supervision

Session 1 Format

INTRODUCTION

The following explanation might be given:

Who am I?
My name is ...I am a Specialist nurse who is trained in helping patients who are attending the Oncology Service and who also have a problem with (low mood) depression.

Purpose of interview
I would like to work with you to see if together we can help you feel better.

What we will cover today
Today I suggest that we devote the next hour or so to reviewing how you are at present. After that, I propose that we meet on up to 7 more occasions to work together on how you might overcome the depression and the problems that are contributing to it.

How long do we have?
We have about an hour. We have a number of things to cover so I may need to interrupt you. Is that OK?

Is there anything you would like to ask at this stage?"
Did you have any worries or concerns about coming today?

Give patient a treatment information booklet (appendix a) and consent form for recording interviews (if using this method for supervision) (appendix b).
Ask patient to complete the PHQ-9 (appendix c) before starting the session.

PATIENT'S BASIC INFORMATION

The first thing I want to do is to find out a little about you and check some basic details:

- Age
- Marital status
- Employment status
- Living arrangements
- Who at home – who provides support?
- GP and how get on with? (remember to check GP contact details)
- Who is the oncologist and how long have they been coming to clinic?

PATIENTS IMMEDIATE CONCERNS

Now I'd like to make a list of all your current concerns. Once we have the list, we can talk about each of these individually.

- Make list of all (at least 3) concerns with brief description of each (but defer detail)

- Ask and be specific about whether they consider loneliness a problem if social support appears limited and add to the list

- Ensure cancer and depression (or equivalent) on list

Say *' anything else' 'can you describe that to me' 'can you give me an example'*
Use empathy *' that must be difficult - was that upsetting?'*

Once list obtained summarize for patient

ENQUIRY ABOUT CANCER

Now I'd like to ask you about your experience of your cancer
Tell me the story of the cancer. (If necessary prompt with...)
- *How did it start?*
- *When was it diagnosed?*
- *How has it been treated?*
- *Ask how do you feel about that?*
- Current Symptoms (list) – ask about pain

What is your current treatment?
- *What drugs and how often?*
- *How effective do you think it will be*

In what way is the cancer a problem for you ***NOW****...?*

How do you feel about your cancer?
When you think about it do you have any particular words or images?
What do you think the cause is? (optional)
Impact of the cancer on your....
- lifestyle
- work
- finances
- family relationships
- social life
- faith

Is there anything you can do?
How effective do you think it will be?

Have you thought about dying?
What is the worst thing for YOU about dying?

How do you see the future *(probe their understanding of their prognosis)*?

ENQUIRY ABOUT DEPRESSION

Understanding of the nature and cause of depression.

I'd now like to ask you about your depression
Tell me the story of the depression. If necessary prompt with...
- *How did it start?*
- *Why do you think you got 'down in the dumps'/low/miserable?* (use the word/term the patient uses to describe their mood)
- *When was it diagnosed?*
- *How has it been treated?*

What is your current treatment?

- *What drugs and how often?* (Precise medication dosages; duration; adherence and helpfulness)
- *How effective do you think it will be?*

*How is the depression a problem FOR YOU **NOW**...?*

Current Symptoms

- List symptoms (use the SCID as guidance, appendix d) and check for suicidality and chart on SCID scoring sheet, also appendix d)
- Check for bipolar disease. *Do you have any episodes that you feel very happy and full of energy? Have you ever had any episodes like that in the past?*

Impact of the depression on your....

- lifestyle
- work
- finances
- family relationships
- social life
- faith

Is there anything you can do yourself?
How effective do you think it will be?
Do you think you can overcome depression?
Have you ever had depression before? (when, duration and how treated)

CURRENT CIRCUMSTANCES

*Now I'd like to ask in a bit more detail about how you are **NOW***

- Other current illness
- ALL current medication/treatment
- Current alcohol intake (units per week)
- Current social support – including shortcomings in network or use of network (important issue so be probing)

BACKGROUND

I'd like to ask you a few more things about your background

- family history of cancer and depression and/or previous experience of illness/cancer
- personal upbringing, occupations and relationships
- Usual personality/ how you usually cope with stress.

Apart from this challenge that you are facing now, can you think of any other challenges you have faced in your life? (be probing – it would be unusual to find a person who hasn't experienced something difficult in their life)
You've obviously coped with things before in your life – how do you usually cope?

CONSTRUCTION OF CURRENT CONCERNS LIST

That has been very helpful because you've now told me that ..... are problems for you, would you say that.....is a problem for you that you may want to add to the list?

- Add any others that emerged during the therapy.
- If the patient has hinted at another concern or it seems to be present, offer that to the patient as a potential concern, which they may wish to endorse.
- Ask and be specific about whether they consider loneliness a problem if social support appears limited and add to the list (i.e. *is loneliness a problem for you?*)

Let's list together your main concerns ***NOW?***
Make sure to check for any other concerns
Once all concerns explored summarize again

OK to summarize...

One problem is the fact that you've got/had cancer.
You've now got a second problem with depression
The other concerns you've told me about are...

- List and clarify each

*********Make sure problems are specific and precisely formulated**********

EXPLAINING THE APPROACH TO TREATMENT

I would like to work with you to help you feel better.

Depression is an illness and can make the cancer feel worse – it makes physical symptoms seem worse, and makes you feel more helpless and pessimistic.

The good news is that we know a great deal about how to help people overcome depression

The word 'depression' can be misleading because it is also used to describe people simply feeling unhappy. In fact depression is a term used to describe a collection of symptoms such as low mood, loss of interest, lack of concentration, poor sleep or feeling irritable (etc - relate to the symptoms the patient has presented with). *It is thought that people may be more vulnerable to developing this collection of symptoms because of genetics or previous experiences in their lives. We know that depression is usually triggered by stress and it is associated with changes in the chemistry of the brain. Once this happens, you may not feel very positive and may feel that you aren't coping as well with the problems in your life. Once the depression has started, it can be kept going by these feelings of hopelessness/loss of control. So depression is related to the way we think about things that happen in our lives and to the way we cope with them.*

So depression is a real illness and the good news is that it is treatable!
There are very successful treatments for depression. The two main ones are antidepressant therapy and talking therapies. Our approach is to offer both together – the antidepressants to reverse the chemical changes in the brain and the talking therapy to help you cope with problems happening in your life and to address the feelings you have as a result of the depression. You will not be forced to accept both however. Both work individually but together are more effective.

The talking therapy component of the treatment is a very practical approach to help you with the way you are coping with problems. This treatment will help you tackle problems which will make you will feel more in control and better able to cope. We call this talking therapy advanced coping skills training. It is also a long-term skill that can help you in the future.

What is involved is that you choose one problem to work on in the session. Once you have generated solutions to the chosen problem, you then choose an achievable solution to try at home before the next session. By doing this, you will become very skilled at coping and therefore more confident that you can influence what happens to you..

As a result, the symptoms of depression that you are experiencing will improve.

Do you have any questions before we move on? (use the FAQ sheet, appendix e), as a guide to answering any questions)

This part of the session will be a bit different from what we have done so far. It is where you do the work. It is the beginning of your advanced coping skills training program. As part of this training I will show you a technique to approaching problems.

ADVANCED COPING WORKSHEET – exercise for depression

The aims of this part of the session are: -

- To review the patients symptoms of depression and their problems,
- To explain the rationale and principles of the advanced coping skills component of the treatment;
- To illustrate the stages of advanced coping using a specific problem such as low mood as an example.

In this session the stages of advanced coping are described to the patient and discussed in detail, so that the patient understands how and why it is likely to help. It is important to motivate the patient to comply with treatment.

Procedure

First, I will summarize the concerns you have told me about and then I will explain how to approach the problem in a new way. There are some concerns on your list that you may consider to be problems for you, which you may want to tackle. But today, I'd like to use the example of your 'low mood'/ depression (use the patient's term for their depression) to illustrate how to use this new technique.

Explain 'advanced coping skills' using the following framework:

Problems
List the problems in a clear and concrete form (suggesting that the first to tackle may be low mood/depression).

Goals
Identify a goal for this problem that is concrete and achievable before the next session. This should be practical e.g. doing one positive thing.

Solutions
Encourage as many solutions to this as he/she can generate. Ensure the following are on the list and discussed...

Antidepressants including eliciting patient's pros and cons – educate where appropriate. Getting anti–depressant drug treatment from the patient's doctor (usually GP but Oncologist if patient rarely sees GP) should be examined as a solution. In this way, the emphasis on the use of antidepressants should not be detrimental to the empowerment of the patient in the 'advanced coping' context.

Pros and cons
The examination of the pros and cons of this solution will bring to light issues about the acceptability to the patient of anti–depressant drugs and provide an opportunity for education using the patient information pack.

Chosen solution and plan
The patient should have a clear set of tasks that need to be completed before the next session, referred to as homework, and listed on the advanced coping skills work sheet (see appendix f). If the patient is already taking antidepressant medication, the patient should be encouraged to chose a solution that will also contribute to 'relieving' the depression (could be as simple as seeing the grandchildren more often or be a form of behavioural activation, see below)

Consider using role-play if the patient lacks confidence about the tasks.

Behavioural activation. Getting going and scheduling pleasurable activities.

In addition to the advanced coping exercise, encourage the patient to consider doing something active they enjoy before the next session eg walk with a friend, going swimming etc (behavioural activation)

At the end of the first session, the nurse should emphasize that much ground has already been covered in that session. The patient doesn't have to remember all this initial material because further explanations will be given in subsequent sessions.

Using and building network of social support

The importance of building a support network should be emphasized at this point to prepare for the end of the sessions. Explain that this will be explored in the next session using the advanced coping technique.

The session concludes with three important 'take home' messages: -

- Depression is an illness that is treatable. It is an illness that causes you to think in a more negative way and makes you feel less able to cope with problems;
- We can't solve the cancer but if other problems important to you can be tackled, the way you think about events in your life alters and the symptoms of depression will improve;
- Specific tasks need to be completed before the next session.

ENDING THE SESSION AND MAKING A PLAN

I'd like you to read the patient information booklet and then to meet with me again in a few days. What do you think? Do you have any questions?

Allow time for the patient to ask questions and clarify issues

BEFORE END OF SESSION

- Ensure agree to a further 5-7 sessions;
- Plan time and place of next appointment (3-4 days following session 1);
- Ensure plan for antidepressants (either starting medication or increasing dose).
  IF AGREED – patient will see doctor;
- Nurse will contact doctor by post/phone.

Session 2 Treatment Focus = Social Support

AIMS:

Review

Last session

Clinical condition – symptoms, state of cancer, treatment and any change or addition to current medication. If the patient has already started antidepressant therapy since session 1, chart type, dose, date started and also any side effects.

Mood state and any suicidality

Homework

- Antidepressants (Acceptability, fears, dose and adherence) or alternative solution for depression
- Behavioural activation

Concerns

Work

Explain the advanced coping skills technique again and work on support and social networks. If however this is not a problem for the patient, work on a problem of the patient's choice with some guidance to choosing a problem that has achievable solutions.

Plan

Homework (Social network -plan for future)

Next appointment for approximately 1 week's time

DURATION: 45 mins max

OUTPUTS: Plan for next problem
Next appointment

HOMEWORK PATIENT: One task – chosen to overcome hopelessness

HOMEWORK NURSE: Complete treatment summary sheet
Discuss in supervision

Session 2 Format

The nurse should check the patient's clinical improvement by asking the patient to complete the PHQ-9 before the start of the session.

REVIEW AND SET THE AGENDA

First, I want to go over the reason for using this therapy again. Then I want to check briefly with you about how you have been feeling since I saw you last – physically and emotionally. Then how you managed with your homework from last time.

Remember I explained that depression is related to the way we think about things that happen in our lives and to the way we cope with them. Symptoms of depression occur when you don't feel positive and you feel that you aren't coping as well with the problems in your life. Therefore if you are able to tackle the problems, you will feel more in control, better able to cope and the symptoms of depression that you are experiencing will improve. Today I want to focus on the way you normally cope with problems, then practise the advanced coping skills technique using a problem of your choosing from your list of concerns.

But first.....

- Ask about reactions to last session; *Any questions about our last session – anything upsetting?*

- Clinical condition – Symptoms; state of cancer and treatment and medication. *How are you getting on? What is happening with your treatment?*

- Mood state and any suicidality - *How are you feeling in your mood? Have you had any thoughts of harming yourself?*

Homework.

- Advanced Coping Skills – check their homework sheet
  Your homework last week was to look at ways of coping with *** (or depression). *How did you get on with this? Did it work? Any problems?* (give huge amounts of praise if they implemented their solution).
  If their solution was Antidepressants. *Did you see your GP? Are you taking antidepressants? Any problem taking them? Any problem with side effects? Do you think that they are helping yet?* Chart type, dose, side effects, instructions given by GP and follow-up arranged by GP.
  (If they didn't achieve the homework then take that as the problem to tackle this session.)

- Behavioural Activation *Are you doing things? Is that helping you feel better? Any problems with this?*

Review concerns – *Let's go over the things that have been concerning you. Let's review our original list. Do you still think it is right? Is there anything you want to change or add?*

COPING SKILLS TRAINING

The technique you practised last week, the advanced coping technique, can be more difficult for some people than others. The reason for this is that there are some things about how you normally cope that can get in the way. It would be worthwhile before we carry on to check if any of these apply to you so that we can be mindful of them as we use the technique.
For instance, it's a bit like going on an advanced driving test. Lets just think of what would stop you getting through the course. You might be the kind of person who shuts their eyes in an emergency – well if we were trying to teach you how to steer out of a scid, the first thing to do would be to make sure you keep you eyes open.
Similarly, things that might make it difficult for people to learn AND use the advanced coping skills technique are things like….

- *a tendency to rush into things without thinking* (impulsiveness)
- *a tendency to rely on other people to sort things out or feeling that you aren't confident enough yourself to tackle problems* (dependency)
- *a tendency to agonise over decisions (indecisiveness)*

How would you describe yourself? Do any of the above apply to you?
*Ok that's very helpful. When you go through your training course we need to be mindful of your tendency to **** , otherwise when you attempt to tackle a problem we might run into trouble.*

We will continue practising the technique called advanced coping skills which you used in the last session.

This will

- *help you improve your skills in tackling problems*
- *increase your sense of control*
- *decrease distress, and therefore….*
- *improve your quality of life*

In this session we will explore a problem that some patients experience that of poor social support, which is in fact an important moderator of stress. In other words, people who have positive social support feel less stressed by problems they encounter.

Social network - Explore social network in detail. Be probing and inquisitive.

So first I want to just ask you about the support you have at the moment…..

Who are you able to talk to about your concerns? Does that help? Any problems here?

(Today you have told me that support and having someone to talk to is limited. Because support is an important part of your recovery and something that needs to be planned in preparation for the end of these sessions, I want you to apply the advanced coping technique to this problem in this session.)

OR

(It seems from what you are telling me that you have a good range of people who you can talk to after these sessions have finished. We will talk about your support again towards the end of this therapy but in today's session, I would like to help you tackle a problem from your list in the way that you did last session.)

Explain the advanced coping technique again with emphasis on the first step of 'defining the problem', working on current problem (social support)

Complete a worksheet on the current problem (support or other), emphasising the importance of defining the problem. Describe this step as gathering information/facts about the problem in the way that a detective would. The clearer the problem, the easier it will be for the patient to generate solutions.

Pretend you are a detective:

- *Gather all the facts*
- *Describe the facts in clear language*
- *Separate the facts from what you think about the situation*

Ask the questions, Who? What? Where? When? How?

HOMEWORK

For your homework this week, I want you to try your chosen solution to addressing the problem of support (or appropriate problem if social support not a problem).

This homework is the basis for next week's session and it is therefore important that you try this. If you find it too difficult, try doing a bit every day.

Session 3 – 5 Treatment
Session 5 focus = formal treatment response assessment

Session 5 = formal review in supervision of treatment response and treatment plan reviewed using treatment algorithm (see appendix g)

AIMS:

Review

Last session

Clinical condition – symptoms, state of cancer, and treatment.

Mood state and any suicidality
Acceptability, dose (and appropriate increase) and compliance with antidepressant medication

Homework
- Activation
- Social network (plan for future) Explore the success of previous session's implemented solution

Concerns

Work
Work on current problem

Plan
Homework
Next appointment for approximately 1 week's time

DURATION: 30-45 mins

OUTPUTS: Plan/homework for target problem
Plan for medication
Return date and time

HOMEWORK PATIENT: Advanced coping task

HOMEWORK NURSE: Review in supervision. Discuss treatment response (formally in session 5 using the treatment modification algorithm (appendix g) and discuss treatment plan with supervisor.

Session 3 – 5 Format

REVIEW AND SET THE AGENDA

The nurse should check the patient's clinical improvement using the PHQ-9 and general progress at the beginning of each session.The patient's coping skills homework should be reviewed at the beginning of each session.

First, I want to check briefly with you about how you have been feeling since I saw you last – physically and emotionally. Then how you managed with your homework from last time.

- Ask about reactions to last session; *Any questions about our last session – anything upsetting?*
- Clinical condition – symptoms state of cancer and treatment. *How are you getting on? What is happening with your treatment?*
- Mood state and any suicidality - *How are you feeling in your mood? Have you had any thoughts of harming yourself?*
  Antidepressants *Are you taking antidepressants? Any problem taking them? Any problem with side effects? Do you think that they are helping?* Chart dose, side effects, effectiveness. If the dose is not at therapeutic level, encourage the patient to consult his/her GP to discuss an increase in dose.

Homework.

- Advanced Coping Skills – check their homework sheet
  *Your homework last week was to look at ***. How did you get on with this? Did it work? Any problems?* (give huge amounts of praise if they implemented their solution). (If they didn't achieve the homework then take that as the problem to tackle this session)

Activation *Are you doing things? Is that helping you feel better? Any problems with this?*

Review concerns
Let's go over the things that have been concerning you. Let's review our original list. Do you still think it is right? Is there anything you want to change? What shall we work on today?

COPING SKILLS TRAINING

The remainder of the time should be spent in coping skills tasks limited to one per session or

HOMEWORK

one over a number of sessions if the problem is complicated.

Set homework relating to a current problem or trial an alternative solution to last session's problem if the chosen solution was unsuccessful or had limited effect.

Plan next appointment for approximately 1 week's time.

Session 6 Treatment
Focus = formulating a relapse prevention plan

Session 6 or penultimate session = development of a relapse prevention plan (appendix h)

AIMS:

Review

Last session

Clinical condition – symptoms, state of cancer, and treatment.

Mood state and any suicidality
Acceptability, dose (and appropriate increase) and compliance with antidepressant medication should be reviewed.

Homework
- Activation
- Explore the success of previous session's implemented solution

Concerns

Work
Work on current problem
Complete the relapse prevention plan

Plan
Homework
Next appointment (for approximately 1 week's time)

DURATION: 30 – 45 mins

OUTPUTS: Plan for target problem
Relapse prevention plan
Plan for medication
Return date and time

HOMEWORK PATIENT: Coping skills task

HOMEWORK NURSE: Review in supervision. Discuss relapse prevention plan with supervisor

Note that supervision for all patients completing session 5 is compulsory. A formal presentation of progress on all patients is required with chart of PHQ scores to assess reduction in score.

Session 6 Format

REVIEW AND SET THE AGENDA

The nurse should check the patient's clinical improvement using the PHQ-9 and general progress at the beginning of the session. The patient's coping skills homework should be reviewed at the beginning of the session.

First, I want to check briefly with you about how you have been feeling since I saw you last – physically and emotionally. Then how you managed with your homework from last time.

- Ask about reactions to last session; *Any questions about our last session – anything upsetting?*
- Clinical condition – symptoms state of cancer and treatment. *How are you getting on? What is happening with your treatment?*
- Mood state and any suicidality - *How are you feeling in your mood? Have you had any thoughts of harming yourself?*
  Antidepressants *Are you still taking the antidepressants? Any problem taking them? Any problem with side effects? Do you think that they are helping?*

  Chart dose, side effects, effectiveness. If the dose is not at therapeutic level, encourage the patient to consult his/her GP to discuss an increase in dose.

Homework

- Advanced Coping Skills – check their homework
  *Your homework last week was to look at ****. How did you get on with this? Did it work? Any problems?* (give huge amounts of praise if they implemented their solution)

  (If they didn't achieve the homework then take that as the problem to tackle this session)
- Activation *Are you doing things? Is that helping you feel better? Any problems with this?*

Review concerns

Let's go over the things that have been concerning you. Let's review our original list. Do you still think it is right? Is there anything you want to change? What shall we work on today?

COPING SKILLS TRAINING

The remainder of the time should be spent in coping skills tasks limited to one per session or one over a number of sessions if the problem is complicated.

RELAPSE PREVENTION PLAN

It is important after this treatment finishes, that you not only use your training in advanced coping skills in the future to prevent problems getting on top of you but also to regularly assess how you feel. Today I want to start looking at your individual plan to stay well. Your plan should include self-monitoring, identification of factors that may make the depression more likely to return (trigger factors) and a plan of action if you suspect the depression is returning. At the back of your patient information booklet you will find a form you can fill in (see appendix h) that covers all these things I have just mentioned. Today we should try and work through this together.

Work through the relapse prevention plan to help the patient identify their first signs and symptoms of depression by referring to the onset of this episode. Identify their trigger factors (such as family problems or deterioration in health). Work through their plan of action should the depression return emphasizing the importance of using the strategies that worked this time and using the new coping technique.

HOMEWORK

Set homework relating to a current problem or trial an alternative solution to last session's problem if the chosen solution was unsuccessful or had limited effect.

Complete the relapse prevention plan if not completed in session.

Plan next appointment for approximately 1 week's time.

Session 7 Treatment Focus= Social Support

AIMS:

Review

Last session

Clinical condition – symptoms, state of cancer, and treatment

Mood state and any suicidality
Antidepressants Acceptability, dose (and appropriate increase) and compliance with antidepressant medication should be reviewed.

Homework
- Activation
- Relapse prevention plan

Concerns

Work
Work on current problem or relapse prevention plan or revisit social support if that was an identified concern
Assessment of understanding of advanced coping skills technique

Plan
Homework
Next appointment (approximately 1 week's time)

DURATION: 30 - 45 mins

OUTPUTS: Plan for target problem
Plan for medication
Return date and time

HOMEWORK PATIENT: Coping skills task

HOMEWORK NURSE: Review in supervision

Session 7 Format

REVIEW AND SET THE AGENDA

First, I want to check briefly with you about how you have been feeling since I saw you last – physically and emotionally. Then how you managed with your homework from last time.

- Ask about reactions to last session; *Any questions about our last session – anything upsetting?*
- Clinical condition – symptoms state of cancer and treatment. *How are you getting on? What is happening with your treatment?*
- Mood state and any suicidality - *How are you feeling in your mood? Have you had any thoughts of harming yourself?*
  Antidepressants *Are you still taking antidepressants? Any problem taking them? Any problem with side effects? Do you think that they are helping?*

Homework

- Advanced Coping Skills – check their homework
  *Your homework last week was to look at ****. How did you get on with this? Did it work? Any problems?* (give huge amounts of praise if they implemented their solution)
  (If they didn't achieve the homework then take that as the problem to tackle this session)
- Activation *Are you doing things? Is that helping you feel better? Any problems with this?*

Review concerns
Let's go over the things that have been concerning you. Let's review our original list. Do you still think it is right? Is there anything you want to change? What shall we work on today?

Review the patient's progress.

Review the patient's coping skills homework and/or development of their relapse prevention.

REVIEW OF COPING SKILLS TRAINING

The progress made by the patient and the lessons they have learned from the training in coping skills should be reviewed.
The relapse prevention plan should be reviewed in session.
Review their support network.
The remainder of the time should be spent in coping skills tasks.

HOMEWORK

Set homework relating to a current problem or trial an alternative solution to last session's problem.

Plan next appointment for approximately 1 week's time – to complete 8-week treatment period.

Session 8 Ending treatment
Focus = Review of relapse prevention plan

AIMS:

Review last session
Review homework
Review mental state including suicidality
Review problem list – what's done & what remains
Review antidepressant medication (attainment of therapeutic dose and adherence)

DURATION: 30-45 mins

OUTPUTS:

Future plan for coping skills
Future plan for medication
Future plan for support
Completed relapse prevention plan

HOMEWORK PATIENT:

See GP and discuss progress and plan

HOMEWORK NURSE:

Review in supervision
Write to GP – discuss on telephone if necessary
Plan further contact options

Session 8 Format

REVIEW AND SET THE AGENDA

First, I want to check briefly with you about how you have been feeling since I saw you last – physically and emotionally. Then how you managed with your homework from last time.

- Ask about reactions to last session; *Any questions about our last session – anything upsetting?*
- Clinical condition – symptoms state of cancer and treatment. *How are you getting on? What is happening with your treatment?*
- Mood state and any suicidality - *How are you feeling in your mood? Have you had any thoughts of harming yourself?*
  Antidepressants *Are you still taking antidepressants? Any problem taking them? Any problem with side effects? Do you think that they are helping?*

Homework

- Advanced Coping Skills – check their homework
  *Your homework last week was to look at ****. How did you get on with this? Did it work? Any problems?* (give huge amounts of praise if they implemented their solution)
  (If they didn't achieve the homework then take that as the problem to tackle this session)
- Activation *Are you doing things? Is that helping you feel better? Any problems with this?*

Review concerns

Let's go over the things that have been concerning you. Let's review our original list. Do you still think it is right? Is there anything you want to change? What shall we work on today?

Review the patient's progress.

Review the patient's coping skills homework and/or development of their relapse prevention plan.

Discuss their plans for future self-help – addressed with coping worksheet on 'support' in session 2 and session 7's discussion.

REVIEW OF TRAINING IN ADVANCED COPING SKILLS

Review original concerns list and the concerns that have been worked on in the coping skills sessions to reinforce the patient's progress/recovery.

- Summarise the concerns outstanding from the original list and explore with the patient their relative importance to their current situation.

- Discuss how their advanced coping skills technique can now be applied to these problems in the same way that they have done in the therapy sessions. Assess their confidence to be able to do this out of therapy.

- Reinforce the three important factors in recovery from depression and their role in preventing another depressive episode.

  The (three) things that have helped in your recovery have been: a talking therapy; (antidepressant medication) and support from other people. If you continue to manage problems that happen in your life using the advanced coping technique, you will be less likely to become depressed again. Your medication is important and should be reviewed regularly by your GP and you should keep him informed of your progress. Also the support available to you if used in the way that we explored in one of the sessions,will help you cope with any future concerns.

FURTHER CONTACT

The basis on which further contact with the nurse will occur should be outlined.

The treatment period has now ended. We have planned how you will continue to actively address your problems and concerns on your own and from whom you will seek support.

It is better for you if you now practice managing any problems you encounter in this way. If you need to contact me for a 'booster' session of what we have done, you can give me a call. In addition to this, I will contact you regularly at monthly intervals to check your progress.

GUIDANCE NOTES 1

SITUATIONS WHEN PATIENTS SHOULD BE DISCUSSED WITH A SUPERVISING PSYCHIATRIST/PSYCHOLOGIST

- Nurse's concern about suicide risk (see guidance notes on suicidality)
- Patient's failure to show any reduction in depression by session 5 as per treatment algorithm, appendix g.
- Difficulties with compliance/tolerance of antidepressant medication.

All the above topics should be brought to supervision. In case of urgent concern, a member of Liaison Psychiatry Service should be contacted the same day. It will be at the Psychiatrist's discretion to whether the patient is seen. Any time the psychiatrist spends seeing the patient will be recorded.

GUIDANCE NOTES 2

PATIENTS WHO ARE SUICIDAL OR HOPELESS

All patients should be assessed at session 1 using the SCID and explicitly asked about suicidal ideation.

In all subsequent sessions, suicidal ideation should be explored.

If any patient whose depression worsens, who expresses hopelessness or a desire to be dead, further questioning should be conducted regarding their suicidal thoughts.

Once suicidal ideation is elicited it should be explored as follows:

- *How often do you have these thoughts?*
- *How strong are they?*
- *What would you do?*
- *Have you ever acted on them?*
- *Do you think you might?*
- *What would make that more likely?*
- *What would make it less likely?*
- *Do you think you are at risk now?*

If after completing the above the nurse has concern that the patient is at risk she should contact the supervising psychiatrist and the patient's GP.

If she thinks that they are at immediate risk she should not leave the patient and call urgently for emergency psychiatric evaluation.

GUIDANCE NOTES 3

MANAGEMENT OF ANXIETY/PANIC

In the case of severe concurrent anxiety disorder, the general approach to treatment should be the same.
Additional specific measures are as follows:

- Ask person what thoughts/fears are associated with the anxiety and discuss/problem solve them.
- Suggest 'worry time' and relaxation for generalized anxiety
- Advise about hazards of avoidance for phobic anxiety
- Explain that anxiety is likely to respond to same treatment as depression and encourage them to persevere.

Where the above measures are insufficient or where anxiety is so severe it is interfering with therapy, seek supervision.

GUIDANCE NOTES 4

CONTACT AFTER THE 8-10 SESSION TREATMENT

It should be made clear to patients that this is a 10-session treatment and that progress will be assessed after that. After the post 8-session assessment the patient should be discussed in supervision.

If at the formal treatment response evaluation at session 5 and at the end of treatment it is clear that they have not improved or are worse, discuss in supervision and prompt them to plan other help and support.

If there is concern about failure to progress the following options may be considered.
1. Supervising nurse to review
2. Refer to other treatment outside the study
3. Review by study psychiatrist/psychologist

If there is any concern about suicide risk, this should be discussed as outlined on guidance sheet 2. The finite nature of the regular face-to-face contact should be spelt out at the beginning of treatment so that future support is placed on the agenda early on.

At the end of the therapy, the basis on which further contact with the nurse will occur should be outlined:

- The patient is invited to contact the nurse at any time after the end of the therapy and 'booster' sessions can be arranged either as face to face or telephone contact.
  If a patient contacts you record this and time spent.
- In addition to this the nurse will contact the patient at regular monthly intervals while the patient remains on study.

The contact should be discussed with the supervisor.

APPENDIX a: PATIENT INFORMATION BOOKLET

What is depression?

When we talk about feeling depressed in the everyday sense, we generally mean we have hit a bad patch and are feeling down.

However the type of depression that you may be experiencing is more severe. In fact it is considered an illness. Depressive illness can affect both men and women of all ages and from all walks of life.

Each person who is depressed will experience it in his or her own particular way. However depression usually affects your mood, thinking, behaviour and physical health.

- People with depressive illness usually (but not always) feel low in mood.
- You may feel bad or negative about yourself, about everything around you and about the future.

1

You may experience some or all of the following:

- Concentration on even simple tasks can be difficult. Making even the smallest decisions can become impossible.
- Everything can become a struggle. Enjoyment of and interest in other people and events, even enjoyment in life itself can be reduced. Consequently you may often find that you are able to do less.

You may

- feel generally less well
- have disrupted sleep, wake early or sleep more than before.
- eat more than usual and gain weight ***or*** eat less and lose weight
- have more aches and pains.
- lack energy.

2

Why do people get depressed?

There are many causes of depression. Sometimes the trigger will be obvious – a bereavement, redundancy or divorce for example. Sometimes the trigger can be an illness such as cancer. Sometimes there may be a build up of many things or, there may be no apparent reason.

Once depression has started it can be self-perpetuating. For example, loss of energy, interest and motivation leads to doing less. Doing less makes life less rewarding and tends to make the depression worse. People with depression can become trapped in this sort of vicious circle.

Another effect of depression is to make you think that nothing can help. You may feel isolated and feel that you should be able to overcome this illness on your own. It can be impossible to imagine things changing in any way. However this is not in fact true. There *are* treatments for depression and they *are* effective.

3

What can be done?

Even though it may be understandable that people with cancer become depressed, it doesn't mean that the depression that comes with cancer cannot be treated. It can. Treatment will help you cope better. There are three treatments that usually help people with a depressive illness:

1. Talking treatments such as Advanced coping skills training. These involve seeing a trained therapist who helps you to get back in control of your life and escape from the vicious circles of depression.
2. Antidepressant medication helps with depression in most cases. These drugs help to reverse the changes in the brain that occur with depression and can help you cope better.
3. Support from others helps you to get your concerns into perspective and lets you talk about your feelings.

4

ADVANCED COPING SKILLS TRAINING

Each of us has developed our own way of coping with difficulties we encounter in life. However we can usually benefit by learning to cope better. Coping better makes us less depressed. One way of doing this is to learn advanced coping skills.

A trained therapist helps you to identify and cope more effectively with the problems you have.

Treatment involves 8-10 weekly sessions. You will be asked to come to the hospital every week. If for any reason you cannot attend, the session will be conducted over the phone. It is important as far as possible to avoid missing sessions.

The way that you think is a three part process made up of feelings, thoughts and actions. How you feel affects how you think and behave. When you are depressed, you may want to change the way that you feel but emotions are not readily controlled. It is actually much easier to change your actions and thoughts. What you do and what you think will in turn change how you feel.

5

You as the patient play the most important part in treatment.
Your problems or concerns will be identified and listed. You and your nurse will then choose one to work on and decide on a goal. During the treatment session you are helped to think of your own possible solutions to a problem and to consider the advantages and disadvantages of each solution. The important part of the treatment is the time between the sessions when you try out a solution of your choosing.

Once practised, this technique for tackling problems can be used to tackle any problems arising in the future even after these sessions have finished.

At first it may seem a big effort to get started but when you achieve something yourself it can be very satisfying.

This sense of success and achievement is the beginning of getting back in charge of your life and overcoming the depressive illness.

6

ANTIDEPRESSANT DRUGS

Antidepressants are drugs that treat depressive illness. They work by helping to restore the right balance of chemicals (neurotransmitters) in the brain. There are several different kinds of antidepressants.

Doctors may well recommend a course of antidepressant drugs for you. Antidepressants are not tranquillizers and do not cause problems with addiction in the same way that tranquillisers do.

Taking an antidepressant *will increase your chances of recovering quickly* and you will find it easier to help yourself in other ways. There is good evidence that antidepressant medication is effective for people who have both depression and a medical condition such as cancer.

Antidepressant therapy usually takes 2-4 weeks before any significant improvement appears (and 2-6 months before maximal improvement occurs). So it is important to persevere with it to get the full benefit.

7

Side effects do occur but are not usually a major problem. Even if you do experience side effects, the longer-term benefits of the medication are likely to outweigh this short-term inconvenience. However, if you find the side effects difficult to live with, you should continue to take the tablets and arrange to see your doctor. He/she may be able to change the tablet to one with fewer side effects.

If the antidepressants do seem to help you should continue to take them for at least 6 months after you start feeling better. If you stop sooner than this the depression may come back.

8

SUPPORT FROM OTHER PEOPLE

Being able to talk to people about what is bothering you can be helpful in overcoming distress. It is often helpful to identify a family member, friend or a partner whom you can call on for extra support.

Whilst you are seeing the nurse you will feel supported by her. Developing a plan for how you will get support after the sessions is very important. It will be discussed early in your treatment.

When people are depressed they often don't want to socialise, even with friends and family. But when you avoid people, you deprive yourself of a source of fulfilment and pleasure, and it's easy to become even more depressed. This leads to doing less and less with others until you feel so depressed that you spend most of your time alone, again another vicious cycle in depression.

Even though it seems hard at first, it is important to work to build and strengthen your 'support system'. This is the circle of people with whom you can talk freely, feel comfortable and seek comfort.

You may wonder who would want to be with you in your present state of mind. There are also some things that can get in the way of being able to speak freely, like having cancer. You may feel guilty about making others upset by talking about your illness.

The question of how to deal with the things that get in the way of your relationships with others is something you can talk about during the treatment sessions.

Also keep in mind that antidepressant medication can increase your energy and decrease your irritability, so taking an antidepressant could help improve the time you spend with other people

How to reduce the risk of depression returning

Most people with depression do get better after several months, or even sooner with effective treatments.
We are all different but we do all have risk factors that can put us at risk of depression recurring.
Unfortunately some people may have another episode of depression in the future. So this means that we need to pay attention to our moods.

Included in this booklet is a plan to help prevent depression recurring. It is something that you have to practice and continue using.
It can be hard initially to think about the way that you felt before you started making changes in your life .By being aware of your thoughts and feelings, you can identify changes in your mood and intervene early, before your depression becomes severe.

Relapse Prevention Plan

Keep doing what works

Eg. Increasing your pleasurable activities
Antidepressant therapy
Using the support of those around you

Identify things in your life that increase stress

Eg. Paying bills

Identify what coping strategies that have worked for you in the past

Eg. Going for a walk, having a bath

Prepare yourself for high risk situations

These may be everyday annoyances
Eg. Falling behind with work **OR**

They could be very stressful events
Eg. Financial problems

Watch for early warning signs

You will have signs that are personal to you
Eg. Avoiding social contact

Self Monitoring Plan

I will monitor myself for symptoms of depression
When_____
Where_____

Personal Warning Signs
I will look for other signs of depression if I find myself:
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

My Booster Plan
If I notice depression returning I will:
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____

The **trigger factors** that I need to be aware of are

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Summary of advanced coping skills technique

Clearly identify the problem
List solutions that may solve the problem
Try a solution out
Assess the results
You may decide to choose another solution and try it out
Reward yourself for the progress

FURTHER INFORMATION

Your specialist nurse will explain the treatment to you in more detail. She is an experienced cancer nurse who has trained in helping cancer patients who are also suffering from a depressive illness. If you have any further questions about this treatment you can discuss them with her.

Your nurse is:

****
Clinical Nurse Specialist
Cancer Research UK
The Edinburgh Cancer Centre
Western General Hospital.
EDINBURGH Tel: ******

The doctor in charge of the depression treatment programme is:
**********,
Consultant in Psychological Medicine,
Western General Hospital.
EDINBURGH Tel: *********

Notes

APPENDIX b: RECORDING CONSENT FORM

RECORDING CONSENT FORM

Supervisors: Dr Michael Sharpe & Vanessa Strong

When we interview people we can't always write down everything they say. We use forms, which help us to score or summarise information that people give us but it is important for us to check from time to time that the forms accurately represent what patients say. To check this we are asking for your permission to audiotape and/or videotape your treatment sessions. If you agree, your nurse will interview you and record your responses on a paper form as usual. She will also tape the interview. The tapes will used to check that information has been accurately recorded and tapes may also be reviewed by the supervising clinician. With your consent, tapes may be used for training purposes.

I do not give permission for treatment sessions to be taped ☐

I give my permission for treatment sessions to be taped ☐

I give permission for the tapes to be used for training other health care professionals ☐

- I understand that I may ask for the tape/camera to be switched off at any time
- I understand that when the recordings have been used for the above purposes they will be erased.

----------	----------	----------
Name of Patient	Date	Signature
----------	----------	----------
Therapist	Date	Signature

APPENDIX c: PHQ-9

Over the last week, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things				
Feeling down, depressed, or hopeless				
Trouble falling or staying asleep, or sleeping too much				
Feeling tired or having little energy				
Poor appetite or overeating				
Feeling bad about yourself, or that you are a failure, or have let yourself or your family down				
Trouble concentrating on things, such as reading the newspaper or watching television				
Moving or speaking so slowly that other people have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
Thoughts that you would be better off dead, or of hurting yourself in some way				

APPENDIX d: SCID Interview and Scoring Sheet

SCID INTERVIEW QUESTIONS

OK, firstly I'd like you to think about your general mood, let's just concentrate on how you've been feeling during the past month (focus on the worst 2 weeks)

1. Depressed mood (most of the day)
Have you been feeling down in the dumps or low at all?
How bad was that?
How low did you feel?
Can you tell me a little more about it? Can you describe how you feel when you are depressed? Do you get emotional, or upset? Do you ever cry? How often?
How much of the time have you felt like that?
Does this low mood last most of the day, nearly ever day?
How long have you been feeling like this?

2. Loss of interest or pleasure
(Explore lack of interest in relation to practical and physical constraints)
Are you still able to enjoy doing things that you used to?
Do you feel that you have lost interest in things that you used to enjoy?
Is there anything that you CAN do now that you still enjoy?
When did you last have a good time?
Have you been able to laugh at anything lately?
How much of the time have you felt like that?
(Is it for most of the day, nearly every day?)
How long have you been feeling like this?

Lets just focus on the worst 2 weeks you've had during that period

3. Weight loss/gain
How was your appetite – are your eating patterns different to how they used to be?
Do you eat more or less than you used to?
Have you lost or gained any weight in the past month?
How much weight would you have gained or lost do you think? (Do you know how much you weigh now?)
Has your appetite been like this most days in the past few weeks?

4. Sleeping patterns
How have you been sleeping over the past couple of weeks?
Do you have trouble falling asleep?
Do you have trouble staying asleep?
Do you wake earlier than usual, how much earlier?
[Are taking sleeping tablets? How long have you been taking them? What was you sleep like before you started taking them?]
How many hours sleep a night are you getting? Is this nearly every night? Is this different to your normal sleeping pattern?

5. Psychomotor agitation or retardation
(must be observable by others)
Have you been feeling fidgety or restless lately? (Do you pace?)
Can you sit and relax, for example in front of the television?
Or have you felt the opposite – more slowed down than usual?
Was this so bad that others have noticed it?
(What about your husband/partner/children/friends – have they noticed these symptoms?)
Have you felt like this most of the day, nearly every day?

6. Fatigue/low energy [note if on chemotherapy]
Over this period of time have you been feeling particularly tired?
Does this tiredness last most of the day?
Do you feel that you have less energy than usual?
Have you felt like this most of the day, nearly every day?

7. Worthlessness, guilt (must have guilt component)
I'm interested in how you feel about yourself at the moment. Has the way that you feel about yourself altered in any way?
Do you feel bad about yourself?
Do you ever feel so bad about yourself that you feel worthless?
Do you feel guilty about anything that you have done or not done?
Have you felt like this most of the day, nearly every day?

8. Lack of concentration/thinking ability
Do you have trouble concentrating? Does your mind ever wander?
What kinds of things do you have trouble concentrating on?
Does this happen nearly every day?
What about watching TV or reading a book?
Do you find it difficult to make decisions or plan ahead?
Have you felt like this most of the day, nearly every day?

9. Suicide risk (KEEP QUESTIONS SIMPLE AND UNCOMPLICATED)
Can you tell me how bad things have got for you?
Have you ever felt that it's not worth carrying on?
Have things been so bad that you thought that maybe you'd be better off dead?

If high risk continue with questions over....

IF SUICIDAL THOUGHTS ARE PRESENT

How often have you had these thoughts?
How strong are these thoughts?

Have you ever made a plan to end your life?
Have you made any preparations to end your life?
Have you ever actually tried to end your life? If so, how?

How likely do you think it is that you would take your own life?

What would make it more likely?
What would make it less likely?
OR What would stop you from doing anything do you think?

Do you feel at risk now?

Who do you have that you can talk to about these feelings?
Have you told your doctor?
Are you alone? [explore]

****

It seems to me that you are at some risk of harming yourself and I'm a bit concerned about that. I'd like to get one of our clinical team in touch with you today to talk more with you. Will you be OK until then?

Check that patient will be at home (refer to suicide management protocol).

SCID CRITERIA AND SCORING

To make a diagnosis of MDD, **five** or more of the following criteria must have been present during the **same 2 week period in the past month** and represent a **change from previous functioning.**
At least one of the five symptoms must be either question **1** or **2** (core symptoms).

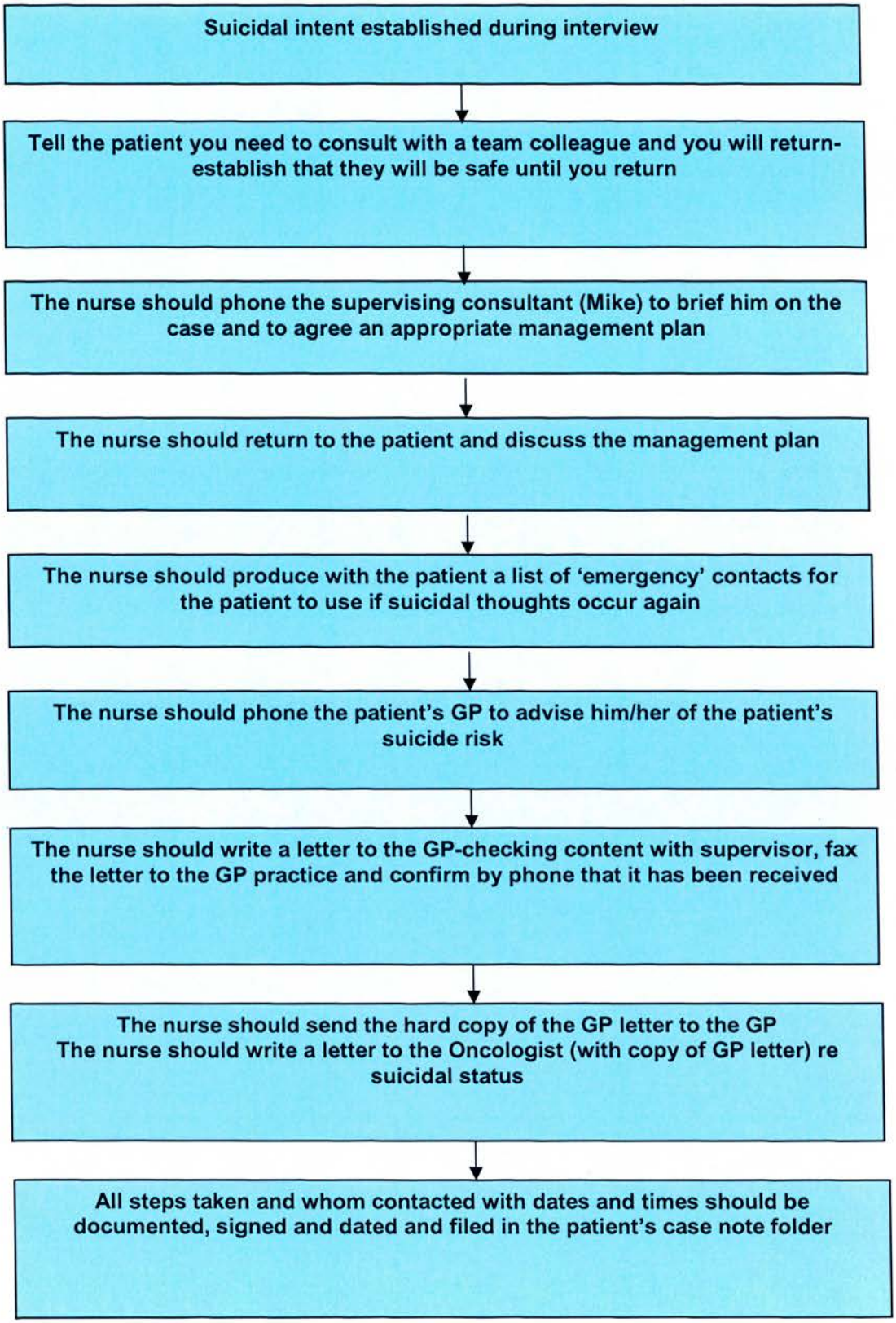
[Scoring: Y = yes (symptom present) N = no (symptom not present)]

CORE SYMPTOMS

1	**Depressed mood most of the day, nearly every day** as indicated either by subjective report (feels sad or empty) or observation (tearful).	**Y**	**N**
2	Markedly **diminished interest or pleasure** in all, or almost all activities most of the day, nearly every day, representing a significant change from previous functioning	**Y**	**N**
3	**Significant weight loss** when not dieting, or **weight gain** (a change of more than 5% in 1 month) OR decrease or increase in appetite nearly every day	**Y**	**N**
4	**Insomnia** or **hypersomnia** nearly every day	**Y**	**N**
5	Psychomotor **agitation or retardation** nearly every day (must be **observable by others**)	**Y**	**N**
6	**Fatigue** OR **loss of energy** nearly every day	**Y**	**N**
7	**Feelings of** worthlessness **OR** excessive **or inappropriate guilt** nearly every day (not merely self-reproach about being sick, or low self-esteem)	**Y**	**N**
8	Diminished ability to **think** or **concentrate** or **indecisiveness**, nearly every day	**Y**	**N**
9	**Recurrent thoughts of death** (not just fear of dying) Recurrent **suicidal ideation without a specific plan**, OR a **suicide attempt** or a **specific plan** for committing suicide (Does not need to be present every day)	**Y**	**N**

TOTAL SCORE ...../9 MDD DIAGNOSIS: YES/NO

Suicide Risk Management Protocol
(Treatment Version)



APPENDIX e: FAQ SHEET

DEPRESSION AND ITS TREATMENT FAQ

1. **What is Depression?**
   The depression we are talking about is an illness. The word depression can be misleading because it is also used to describe people simply feeling unhappy.

2. **What causes depression?**
   People may be more vulnerable to developing the illness because of genetics or pervious experience in their life, it is usually triggered by stress and it is associated with changes in the chemistry of the brain. It is a real illness and the good news is it is treatable.

3. **But I am not the sort of person to develop depression (I am a coper)?**
   Anybody can develop depression. In your case you have had some particularly severe stresses to cope with. Depression is not a sign of weakness it's an illness.

4. **But I should be able to cope with depression myself?**
   Whilst there are things you can do to help yourself get better, it is unrealistic to think that you can just pull yourself out of depression by will power alone. Many famous people with extreme will-power (e.g. Winston Churchill) also suffered depression.

5. **How do antidepressant drugs work?**
   Antidepressants drugs work by reversing the chemical changes in the brain associated with depression. That is they help to make the brain chemistry more normal.

6. **How long do you need to take antidepressants for?**
   The first thing to say is that antidepressants take up to two months before they have their beneficial effects, therefore it is important to take them for at least this long to give them a fair trial. If they are helpful there is no set answer to how long you should take them, but most people would suggest that at least six months.

7. **Aren't antidepressant drugs addictive?**
   That depends what you mean by addictive. In the sense that people need to increase the dose or go seeking illicit supplies they are certainly not. In a sense that a small number of people taking some of these drugs develop usually transient unpleasant symptoms, if they stop them suddenly, they may be or at least some of them may be. In practice we find this really is not a major problem. The one drug that has been pointed to as causing these "withdrawal symptoms" is paroxetine, so if you are particularly concerned about these it is best to choose another drug. There are many to choose from.

8. **Which antidepressant drug should I take?**
   There are a number of antidepressant drugs. The one that is best for you is worked out largely by trial and error. This means that if the first drug doesn't suit you after a reasonable trial it is worth considering changing to another. The drugs are probably all more or less equally effective although if you or your family have had a good response to a particular drug it may mean that that one is most likely to help you. Otherwise we choose the drugs mainly on their other actions. For example some are sedative, and these are particularly useful taken at night for those who have difficulty getting off to sleep. On the other hand people who tend to feel sleepy or drowsy are better taking one that is a little bit more stimulating. Similarly some tend to cause an increase in appetite and weight, and some a decrease. By considering these things it is possible for you and

your doctor to make the best guess first choice, and also to think of what be an alternative should that one not suit you.

9. **What is the point of the talking treatment (the problem solving)?**
   It has been known for a long time that talking treatments can help people get better from depression. That is because once a depressive illness has started it can be kept going by feelings of being helpless and hopeless about the problems one faces. Problem solving works not by solving all your problems (that would be impossible) but by giving you the skills to tackle problems effectively so that you feel more in control and less helpless. The other benefit of problem solving is that it is a long-term skill that can help you in the future.

10. **How do I learn problem solving?**
    You will learn problem solving with the help of the nurse/therapist. Learning problem solving is as much learning a skill, as it is a treatment. That is, you will be given things to read and things to do, you will try them out as "homework" and come back to see your therapist who will act in part like a teacher. And don't worry if learning has not always been easy for you because almost any one can learn problems solving the main thing is to have supervised practice.

11. **Why take an antidepressant drug and do problem solving?**
    It is possible that either treatment alone could help you recover from the depressive illness. However, many years of research has shown that both treatments together are better than either alone.

APPENDIX f: COPING WITH CONCERNS WORK SHEET

Date:

Session:

What is the Problem?

What are my Goals?

Solution	Pros	Cons

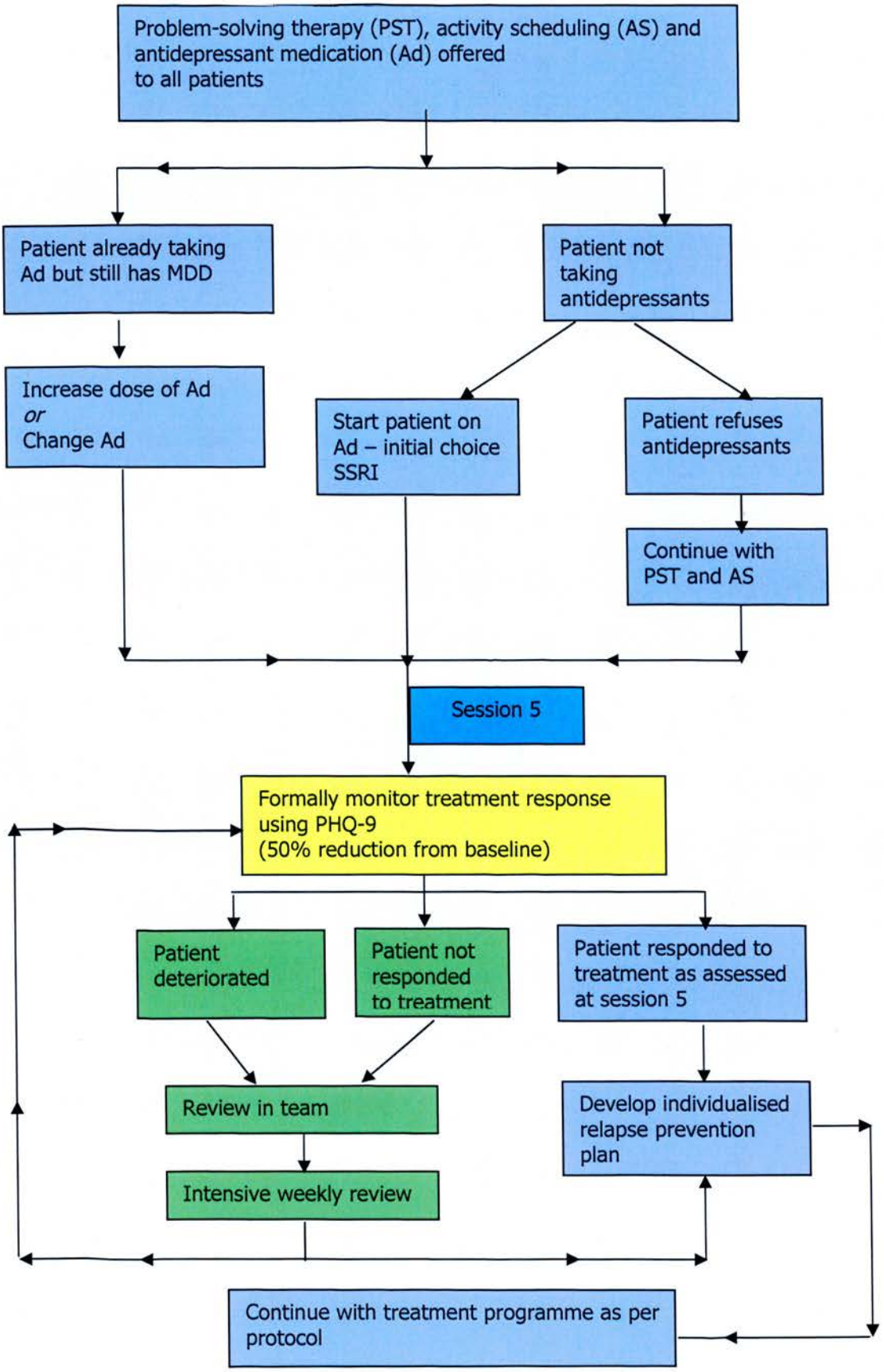
Solutions to achieve goals:

Choice of Solution:

Steps I need to take to achieve this solution:

Things that would stop me achieving this:

Appendix g: Treatment Guideline Algorithm



Appendix h: Relapse Prevention Plan

Self Monitoring Plan

I will monitor myself for symptoms of depression
When_____
Where_____

Personal Warning Signs
I will look for other signs of depression if I find myself:
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

My Booster Plan
If I notice depression returning I will:
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____

The **trigger factors** that I need to be aware of are

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Summary of advanced coping skills technique

Clearly identify the problem
List solutions that may solve the problem
Try a solution out
Assess the results
You may decide to choose another solution and try it out
Reward yourself for the progress

Appendix B: Severity Measure - PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things				
Feeling down, depressed, or hopeless				
Trouble falling or staying asleep, or sleeping too much				
Feeling tired or having little energy				
Poor appetite or overeating				
Feeling bad about yourself, or that you are a failure, or have let yourself or your family down				
Trouble concentrating on things, such as reading the newspaper or watching television				
Moving or speaking so slowly that other people have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
Thoughts that you would be better off dead, or of hurting yourself in some way				

NHS Lothian

CANCER RESEARCH I
Scotl:

THE UNIVERSITY OF EDINBURGH

SMaRT about Cancer

MULTI-COMPONENT NURSE-DELIVERED INTERVENTION FOR MAJOR DEPRESSIVE DISORDER IN PATIENTS WITH CANCER:

A RANDOMISED TRIAL

QUALITY CONTROL PROTOCOL

Protocol Version Number 0.1
Protocol Date: 11.03.04

CONTENT

INTRODUCTION .....

SECTION 1 INTERVENTION TRAINING .....

SECTION 2 INTERVENTION DELIVERY .....

SECTION 3 ADHERENCE MONITORING .....

SECTION 4 APPENDICES .....

List of Figures

Figure 1: COMPETENCY ASSESSMENT
Figure 2: TREATMENT INTEGRITY ASSESSMENT

Appendices

APPENDIX 1: ..... TREATMENT MANUAL ADHERENCE SCORING SHEET
APPENDIX 2: ..... TREATMENT INTEGRITY ASSESSMENT FORM
APPENDIX 3: ..... TREATMENT INTEGRITY ASSESSMENT RESULT FORM

INTRODUCTION

Quality control for the trial intervention will consist of quality control of both the training and of the delivery of the treatment.

Training will be delivered according to the training protocol outlined in this document and competency assessed in a consistent way using a predefined protocol.

On-going quality control will be provided in the form of weekly supervision by the consultant psychiatrist and senior clinical nurse specialist. The focus of the supervision for the treating nurses will be adherence to the research protocol, adherence to the treatment model and discussion of problems arising during treatment.

In addition to this, quality control of the treatment delivery will be assessed formally every 3 months using a structured assessment of each of the components of the treatment, outlined in Figure 2. Adherence to the treatment manual and appropriate use of communication techniques will be assessed by the supervising clinicians on a randomly selected sample of 5 treatment sessions. Adherence will be measured on session specific items using a Likert-type scale rating of 1 to 3 (low to high) as used by Katon et al 1996. The criterion for adherence to the treatment manual is attainment of a score at or above the predefined session threshold scores in ≥ 25 sessions out of 30 (to achieve a total of 30 sessions reviewed over the time of the study intervention (24 months).

SECTION 1

INTERVENTION TRAINING

1.1 Training Protocol

The training programme is outlined below in the order in which it should be delivered. In turn, each component of the programme is outlined in flow diagram format with details of the structure and methods of competence assessment.
Training in each of the components is delivered by a trained therapist.

Communication and Interview Skills training
Communication Skills training session on interview management, interview techniques and eliciting concerns
Face-to-face role-play (video-taped) of eliciting concerns of a cancer patient
Critical review of tape by supervisor
Face-to-face role-play (video-taped) of unstructured interview of a cancer patient
Critical review of tape by supervisor
Role-play (video-taped) + critical review is repeated until competency is achieved

Suicide Assessment & Management training
Training session on risk assessment of suicidal patients
Face-to-face role-play (video-taped) of suicide risk assessment interview
Critical review of tape by supervisor
Training session on suicide risk management
Role-play + (video-taped) critical review is repeated until competency and adherence to the suicide risk management protocol is achieved

(see Appendix d of Treatment Manual for Suicide Risk Assessment interview questions and Suicide Risk Management Protocol)

SCID assessment training
Training session on DSM1V diagnostic interview for depression (SCID)
Face-to-face role-play (video-taped) of SCID interview
Critical review of tape by supervisor
Role-play of telephone SCID interview (audio-recorded)
Critical review of tape by supervisor
(see Appendix C for SCID interview questions and scoring sheet)
THEN (after deemed competent in the above)
5 consecutive SCID interviews with real patients conducted and scored over the phone (audio-taped)
Interviews scored by second rater for inter-rater reliability
Competency is defined as 100% inter-rater SCID scoring concurrence

Overall competency in conducting a SCID interview is:
competency in conducting and scoring a telephone SCID interview with a 'live' patient
+
achievement of 100% inter-rater reliability (assessed on 5 interviews)
+
competency in suicide risk assessment and management

Antidepressant medication
Tutorial on depression and the use of antidepressants + reading material
Face-to-face role-play (video-taped) of interview with patient where an explanation of depression and answers to questions posed by patients is required
Critical review of tape by supervisor
Role-play + critical review is repeated until competency is achieved
Competency is achieved when an adequate explanation of depressive illness can be given and questions answered adequately + an adequate knowledge of antidepressants, their main side effects and main contra-indications as assessed by written or taped aural examination

Case management
Training session on active case management.
Information recording: Training in recording of relevant information
Accurate record-taking of information is assessed against a video-taped patient treatment session.
Written communication: Competency assessment of letter-writing is conducted
Verbal communication: Face-to-face role-play (video-taped) of case discussion with 'real' Oncologist. Competency assessed on ability to answer questions from the Oncologist

Self management
Tutorial and discussion on techniques for effective time management, on the function of supervision and on therapeutic relationship monitoring.
Competency assessment not applicable

Adherence to treatment manual
Tutorial on importance of adherence and on the methods employed to conduct adherence checks
Adherence check performed on a minimum of 12 sessions on the last 2 patients treated using the treatment manual adherence assessment detailed in section 2.3
The adherence check will therefore be performed on 2 full treatment programmes of which there will be 2 session 1s, and 2 relapse-prevention treatment sessions
Adherence is:
Acceptable adherence score in 2 session 1s and 2 relapse prevention sessions
+ acceptable adherence score in at least 7 of the other 8 sessions

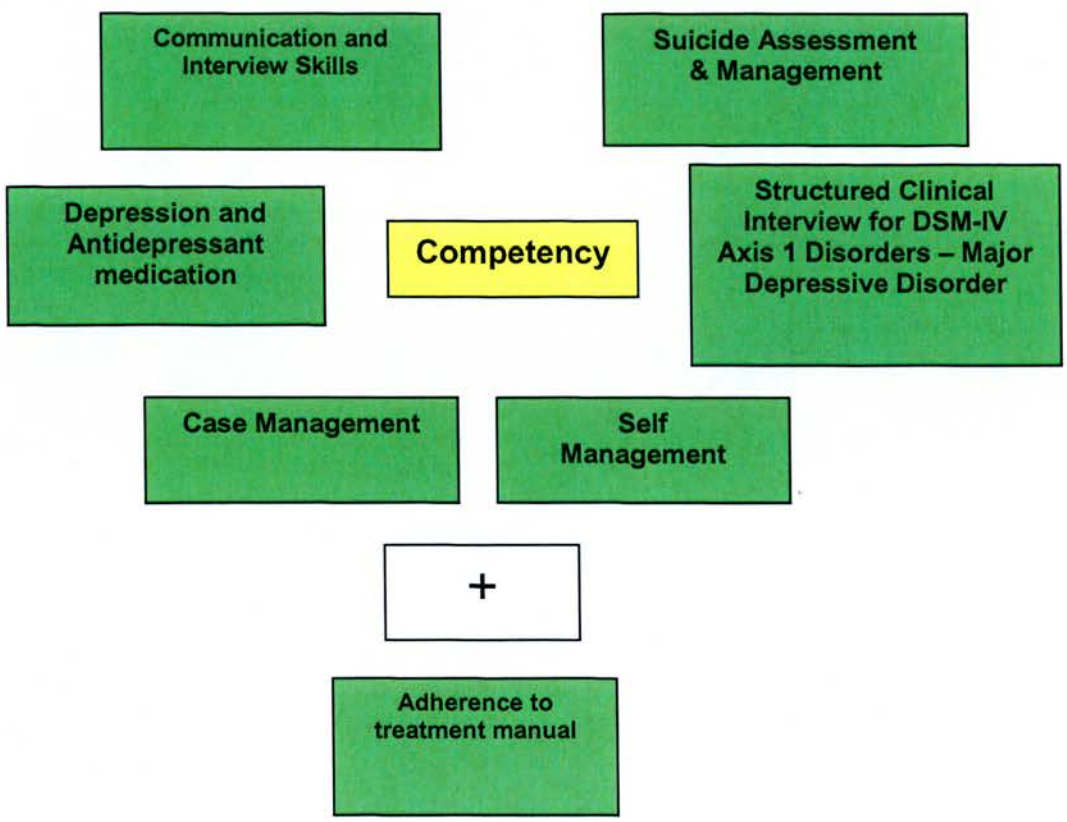
1.2 Duration

The training programme is based on 6 months at 25 hours per week.

1.3 Competency Assessment

Competency must be achieved in each of the components of the training programme shown in Figure 1 in the order outlined in section 1.1 in addition to demonstration of adherence to the treatment manual (as detailed in section 2.1). Competency must be achieved in communications skills before proceeding to training in suicide assessment and SCID diagnostic interviews. The time required to complete this training is approximately 2 months. Following this, training in all other components and in the treatment intervention can proceed which allows 4 months of training to include the treatment of 5 patients.
At the end of the training period, adherence to the treatment manual is formally assessed on the last 2 patients treated.

Figure 1: Components of the competency assessment



SECTION 2

INTERVENTION DELIVERY

2.1 INTERVENTION ADHERENCE PROTOCOL

Intervention Programme
Treatment duration: (max 10 sessions over max 13 weeks; session duration S1 = max 90 mins, S2-8 = max 45 mins)
Adherence to treatment guideline (see appendix g of Treatment Manual): Score on the PHQ-9 should be calculated weekly monitoring for a 50% drop in score from baseline.
Treatment follow-up: Monthly telephone contact

Treatment manual & Communication skills
Treatment manual adherence scoring sheet used which includes communication skills techniques, (see Appendix 1 for Treatment Manual adherence scoring sheet). Criterion for adherence is adherence in ≥ 25 sessions out of 30.

Case management
Active specialist nurse case management - GP liaison + Cancer Care Team liaison

Suicide risk management
Protocol for assessment
Protocol for management

Supervision
Patient's progress presented weekly + adherence to treatment guideline with formal review presentation at session 5.

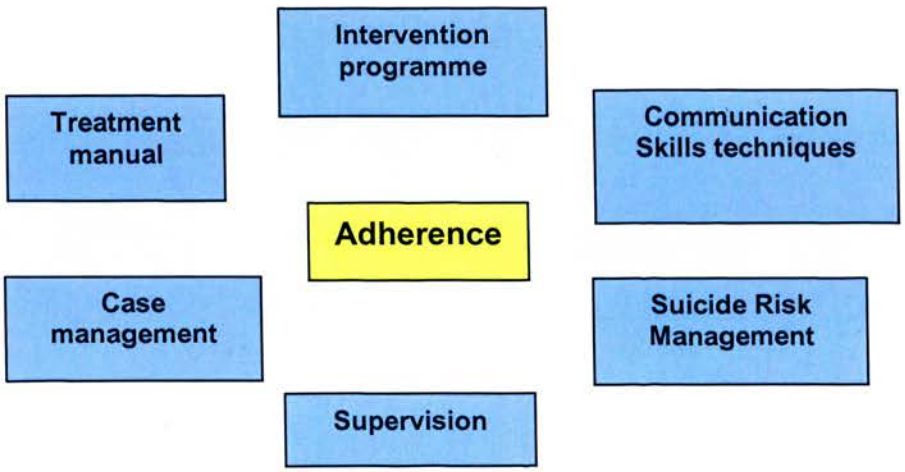
2.2 TIMING

Formal documented adherence checks will be conducted every 3 months. Adherence to the treatment manual will be assessed on a randomly selected sample of 5 sessions every 3 months (to achieve a total of 30 sessions reviewed over the time of the study intervention [24 months] using the criteria for adherence which is adherence in ≥ 25 sessions out of 30).

2.3 TREATMENT INTEGRITY ASSESSMENT

Treatment integrity is confirmed if adherence is achieved in all the components listed in Figure 2 and detailed in section 2.1 and documented using the treatment integrity assessment form (appendix 2).

Figure 2: Components of the treatment integrity validation assessment



SECTION 3

ADHERENCE MONITORING

3.1 TREATMENT INTEGRITY MONITORING

Following each treatment integrity assessment, formal feedback will be given to the therapist by the clinical supervisor(s) using the treatment integrity assessment result form (appendix 3). Any points requiring attention will be discussed and a training plan agreed.

Should the therapist fail to meet the required criteria for adequate adherence to the trial intervention protocol as detailed in section 2.3, this will be discussed with the supervisor(s) and a remedial plan agreed and documented.

If the failure in adherence is due to therapy content (i.e. drift from the treatment model prescribed in the treatment manual), re-training will be organised and a formal competency check carried out as detailed in section 1.3 and Figure 1. During this period it will be at the discretion of the supervisor whether treatment of patients within the trial should continue.

Should the therapist be deemed suitable to continue treating patients, the therapist will be given a reduced patient caseload and a plan of close monitoring shall be agreed and documented. This may involve assessment of a block of treatment sessions or of each treatment session and formal assessment and feedback before continuation of the next treatment session is permitted.

Should the therapist be deemed unsuitable to continue treating patients, the remedial plan will include re-training and formal assessment of competency and the therapist will not be permitted to treat patients during the re-training period.

In any event, should the therapist fail to meet the competency assessment after every reasonable effort has been made to re-train the therapist, the therapist will cease to treat patients and be replaced.

SECTION 4

APPENDICES

Appendix 1: Treatment Manual adherence measure scoring sheet

SESSION 1

Adherence rating (low 1 to high 3)

1 2 3

Introduction (setting the agenda)
- Who I am, my training, who I help
- Purpose of the intervention -To work with you.....
- Time -We have around an hour .....
- Plan - Weekly contact for .....
- Answers any questions

Gives:
- Patient information booklet
- Recording consent
- PHQ9

Basic information
- GP relationship

Concerns
- Listing of immediate concerns
- Probing of loneliness and support
- Summarising of list

Cancer History
- Identifies difficulties about the cancer diagnosis or treatment
- Elicits problems NOW caused by the cancer
- Identifies impact of the cancer using checklist
- Checks with patient whether any of the above problems should be added to the concerns checklist

Low Mood/Depression History
- When started
- When/Whether diagnosed/treated
- Current treatment, dosage, duration, adherence and effect

Previous depression history
Check for sense of control...Is there anything
you can do yourself to overcome depression
Elicits problems NOW caused by the depression
Identifies impact of the depression using checklist
Checks with patient whether any of the above problems
should be added to the concerns checklist

Diagnosis and identification of the nature of the patient's depression

SCID with specific interrogation of following items:
- Mood
- Interest
- Suicidal ideation
- Previous suicide attempts

Current Circumstances
- Checks for any other medication
- Checks for any other current illness, medication, treatment
- Current social support, nursing etc

Background
- Elicits method of coping with life events

Construction of Current Concerns
- Summarises and asks patient for any additions to list
- Proposes additions noted from assessment
- Adds the depression to the list

Adequate explanation of treatment covering the following points
- Collaborative approach – patient and nurse
- Depression is a real illness and is treatable
- Explanation of the main treatment options available
- Explanation of role of support

Checks for questions and uses FAQ sheet for guidance

Adequate explanation of the treatment intervention covering the following points
- Tackling problems by reducing them to smaller parts
- Explanation of the coping skills technique

Advanced Coping Skills Example
- Explains the worksheet
- Uses example of depression
- Technique
  - Defines problem adequately
  - Elicits exhaustive list of solutions
  - Examines pros and cons of each solution
  - Sets homework agreeing date/time
  - Checks for barriers to achieving homework

Gives patient encouragement and praise
following completion of worksheet

Encourages behavioural activation

Discusses support network briefly

Ending the session and making a plan
- Checks with patient for any questions
- Agrees to further 5-7 sessions
- Sets date and time for next session
- Agrees set homework

Summarises what depression is

Summarises why doing advanced coping skills training will help

After session:
Completes GP and Oncologist letters
Writes up assessment
Presents case for discussion in supervision

General non-session specific adherence items

Interview Management	Yes	No
Set agenda		
Used signposts		
Re-focused patient		
Adhered to time		
Duration of session:		

Communication techniques		
Engaged the patient		
Used empathic style		
Used open questions		
Used silence		
Used simple questions		
Asked for clarification		
Used reflection		
Used hypothesis testing		
Used summarising		
Used leading questions		
Used multiple questions		

Assessed by: .....

Signed: .....

Date:.....

SESSION 2 - 4

Adherence rating
(low 1 to high 3)

1 2 3

Administration of process measure (PHQ-9)

Enquires about changes in clinical condition from previous week

Enquires about mood state this week with specific interrogation of following items:
- Mood
- Suicidal ideation

Enquires about antidepressant medication
- Dose
- Dose adherence
- Side effects

Reviews homework from previous week

Checks on progress in behavioural activation

Gives praise on successful completion of homework

Checks for new concerns

Explores specifically social support issue

Completes advanced coping skills worksheet on next problem (social support or other)

Technique
- Defines problem adequately
- Elicits exhaustive list of solutions
- Examines pros and cons of each solution
- Sets homework with date/time if appropriate
- Checks for barriers to achieving homework
- Encourages behavioural activation

Ending the session and making a plan
- Checks with patient for any questions
- Sets date and time for next session
- Agrees set homework

After session:
- Writes up session notes
- Presents progress for discussion in supervision

General non-session specific adherence items

Interview Management	Yes	No
Set agenda		
Used signposts		
Re-focused patient		
Adhered to time		
Duration of session:		

Communication techniques
- Engaged the patient
- Used empathic style
- Used open questions
- Used silence
- Used simple questions
- Asked for clarification
- Used reflection
- Used hypothesis testing
- Used summarising
- Used leading questions
- Used multiple questions

Assessed by: .....

Signed: .....

Date:.....

SESSION 5

Adherence rating
(low 1 to high 3)

1 2 3

Administration of process measure (PHQ-9)

Enquires about changes in clinical condition from previous week

Enquires about mood state this week with specific interrogation of following items:
- Mood
- Suicidal ideation

Enquires about antidepressant medication
- Dose
- Dose adherence
- Side effects

Reviews homework from previous week

Checks on progress in behavioural activation

Gives praise on successful completion of homework

Checks for new concerns

Explores specifically social support issue

Completes advanced coping skills worksheet on next problem (social support or other)

Technique
- Defines problem adequately

Elicits exhaustive list of solutions
Examines pros and cons of each solution
Sets homework with date/time if appropriate
Checks for barriers to achieving homework
Encourages behavioural activation

Ending the session and making a plan
Checks with patient for any questions
Sets date and time for next session
Agrees set homework

After session:
Formal assessment of progress
Presentation of case to supervising psychiatrist
Reduction in PHQ-9 score discussed
Management plan agreed with supervisor

General non-session specific adherence items

Interview Management	Yes	No
Set agenda		
Used signposts		
Re-focussed patient		
Adhered to time		
Duration of session:		

Communication techniques		
Engaged the patient		
Used empathic style		
Used open questions		
Used silence		
Used simple questions		
Asked for clarification		
Used reflection		
Used hypothesis testing		
Used summarising		
Used leading questions		
Used multiple questions		

Assessed by: .....

Signed: .....

Date:.....

SESSION 6 (or penultimate session)

Adherence rating
(low 1 to high 3)

1 2 3

Administration of process measure (PHQ-9)

Enquires about changes in clinical condition from previous week

Enquires about mood state this week with specific interrogation of following items:
- Mood
- Suicidal ideation

Enquires about antidepressant medication
- Dose
- Dose adherence
- Side effects

Reviews homework from previous week

Checks on progress in behavioural activation

Gives praise on success completion of homework

Checks for new concerns

Formal assessment of progress discussed with patient, specifically:
- Reduction in PHQ-9 score discussed
- Management plan agreed with supervisor discussed

Explains the relapse prevention plan

- Completes relapse prevention worksheet

Technique
- Identifies & charts the patient's presenting symptoms
- Identifies & charts the patient's depression trigger factors
- Identifies & charts strategies that have improved the depression
- Develops action plan for detection of return of depression
- Develops action plan for treatment of future depression

Sets homework:
- Further development of the relapse prevention worksheet
- Encourages behavioural activation

Ending the session and making a plan
- Checks with patient for any questions
- Sets date and time for next session
- Agrees set homework

After session:
- Writes up session notes
- Presents progress for discussion in supervision

General non-session specific adherence items

Interview Management	Yes	No
Set agenda		
Used signposts		
Re-focused patient		
Adhered to time		
Duration of session:		

Communication techniques		
Engaged the patient		
Used empathic style		
Used open questions		
Used silence		
Used simple questions		
Asked for clarification		
Used reflection		
Used hypothesis testing		
Used summarising		
Used leading questions		
Used multiple questions		

Assessed by: .....

Signed: .....

Date:.....

SESSION 7 (or final session)

Adherence rating (low 1 to high 3)

1 2 3

Administration of process measure (PHQ-9)

Enquires about changes in clinical condition from previous week

Enquires about mood state this week with specific interrogation of following items:
- Mood
- Suicidal ideation

Enquires about antidepressant medication
- Dose
- Dose adherence
- Side effects

Reviews homework from previous week

Checks on progress in behavioural activation

Gives praise on success completion of homework

Checks for new concerns

Reviews the relapse prevention plan

Reviews the worksheet for social support
Plans strategy for future social support beyond the treatment

Ending the treatment and making a plan
- Checks with patient for any questions
- Reinforces importance of regular monitoring of mood
- Reinforces importance of relapse prevention plan
- Agrees monthly monitoring phone calls

After session:
- Writes up session notes
- Completes GP and Oncologist letters
- Presents progress for discussion in supervision

General non-session specific adherence items

Interview Management	Yes	No
Set agenda		
Used signposts		
Re-focused patient		
Adhered to time		
Duration of session:		

Communication techniques		
Engaged the patient		
Used empathic style		
Used open questions		
Used silence		
Used simple questions		
Asked for clarification		
Used reflection		
Used hypothesis testing		
Used summarising		
Used leading questions		
Used multiple questions		

Assessed by: .....

Signed: .....

Date:.....

Appendix 2: Treatment Integrity Assessment Form

To be conducted every 4 months
Name of therapist: .....
Adherence check No: ..... Time period: .....
Assessed by: ..... Date of assessment: .....

Treatment Programme
(Assessed on a randomly selected sample of 2 patients treated during the previous 4 months)

		Yes	No
Treatment duration	Max 10 sessions Max 13 weeks		
Session duration	S1 max 90 mins S2-10 max 45 mins		
Any additional suicide risk assessment time required?			
Treatment follow-up	Monthly telephone sessions Max 45 mins		

Treatment Manual & Communication Skills
(Assessed on a randomly selected sample of 6 treatment sessions of which at least 1 should be an assessment session + 1 a relapse-prevention session)

	Yes	No
Adherence achieved in 5 of 6 sessions reviewed		

Case Management
(Assessed on documentation for a randomly selected sample of 2 patients)

	Yes	No
Adherence achieved		

Suicide Risk
(Assessment on all cases of patients with high risk)

	Yes	No
Adherence to suicide risk assessment protocol		
Adherence to suicide risk management protocol		

Supervision
(Assessment from on-going monitoring)

	Yes	No
Appropriate use of supervision		
Weekly case presentation (formal case review at S5)		
Adherence to the treatment guideline		

Notes:.....
.....
.....

Appendix 3: Treatment Integrity Assessment Result Form

To be conducted every 4 months Name of therapist: Adherence check No: Time period: Assessed by: Date of assessment:

Treatment Programme
Agreed development target:

Signature ..... Date.....

Treatment Manual & Communication Skills
Agreed development target:

Signature ..... Date.....

Case Management
Agreed development target:

Signature ..... Date.....

Suicide Risk
Agreed development target:

Signature ..... Date.....

Supervision
Agreed development target:

Signature ..... Date.....

Additional Notes:
Agreed development target:

Signature ..... Date.....

Signature of Adherence Assessor ..... Date.....

Appendix D: Self-report Trial Outcome Measures

EORTC-QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers.

	Not at all	A little	Quite a bit	Very much
Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?				
Do you have any trouble taking a long walk?				
Do you have any trouble taking a short walk outside of the house?				
Do you need to stay in bed or a chair during the day?				
Do you need help with eating, dressing, washing, yourself or using the toilet?				

During the past week:

	Not At All	A Little	Quite a Bit	Very Much
Were you limited in doing either your work or other daily activities?				
Were you limited in pursing your hobbies or other leisure time activities?				
Were you short of breath?				
Have you had pain?				
Did you need to rest?				
Have you had trouble sleeping?				
Have you felt weak?				
Have you lacked appetite?				
Have you felt nauseated?				
Have you vomited?				
Have you been constipated?				
Have you had diarrhoea?				
Were you tired?				

EORTC continued.....

During the past week:	Not at all	A little	Quite a bit	Very much
Did pain interfere with your daily activities?				
Have you had difficulty in concentrating on things, like reading a newspaper or watching television?				
Did you feel tense?				
Did you worry?				
Did you feel irritable?				
Did you feel depressed?				
Have you had difficulty remembering things?				
Has your physical condition or medical treatment interfered with your <u>family</u> life?				
Has your physical condition or medical treatment interfered with you <u>social</u> activities?				
Has your health or medical treatment caused you financial difficulties?				

For the following questions please circle the number between 1 and 7 that best applies to you

How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

SCL-20 Depression scale

The next questions ask about how much you were distressed by various symptoms in the past month. The categories are: Not at all, a little bit, Moderately, Quite a Bit and Extremely.
Overall, in the **past month** how much were you distressed by...

	Not at all	A little bit	Moderately	Quite a bit	Extremely
Feeling lonely or blue					
Feeling hopeless about the future					
Feeling no interest in things					
Inability to take pleasure in things					
Poor appetite					
Overeating					
Trouble falling asleep					
Awakening in the early morning					
Sleep that is restless or disturbed					
Thinking, speaking and moving at a slower pace					
Feeling so restless you couldn't sit still					
Thoughts of death or dying					
Thoughts of ending your life					
Feeling low in energy or slowed down					
Feeling everything is an effort					
Blaming yourself for things					
Feelings of worthlessness					
Feelings of guilt					
Trouble concentrating					
Difficulty making decisions					

SCL-90 Anxiety Scale

Over the <u>last week</u>, including today,
HOW MUCH WERE YOU DISTRESSED BY:

	Not at all	A little bit	Moderately	Quite a bit	Extremely
Nervousness or shakiness inside					
Trembling					
Suddenly scared for no reason					
Feeling fearful					
Heart pounding or racing					
Feeling tense or keyed up					
Spells of terror or panic					
Feeling so restless you couldn't sit still					
The feeling that something bad is going to happen to you					
Thoughts and images of a frightening nature					

Coping measure Items:

The next question asks how confident you feel NOW.

On a scale of 0 to 10, where 0 means "not at all confident" and 10 means "extremely confident", circle the number that best represents your answer to the following questions.

How confident are you in your ability to overcome or control an episode of depression?

0	1	2	3	4	5	6	7	8	9	10
NOT AT ALL CONFIDENT										**EXTREMELY CONFIDENT**

The next few questions have to do with strategies you normally use to solve problems. Tick the box that best describes your answer to the following statements:

THINKING OF NOW.....	Not at all	Slightly true	Moderately true	Very true
When my first efforts to solve a problem fail, I know if I persist and do not give up easily, I will be able to eventually find a good solution.				
When I am trying to solve a problem, I get so upset that I cannot think clearly.				
When I have a decision to make, I weigh the consequences of each option and compare them against each other.				
When I am attempting to solve a problem, I go with the first good idea that comes to mind.				
When a problem occurs in my life, I put off trying to solve it for as long as possible.				
Amongst the people I know, there is someone I can go to for support.				
If I needed to, I would go to this person for support.				

Satisfaction with care questionnaire

Over the last 6 months how would you rate the quality of care you have received for **your depression**?

Please tick only one box

No care received ..... ☐

Can't answer ..... ☐

Poor ..... ☐

Fair ..... ☐

Good ..... ☐

Very good ..... ☐

Excellent ..... ☐

Appendix E: Data collection form and data definitions

NB Take all clinical data as at date of positive MDD diagnosis on SCID	
Date of 1st primary cancer diagnosis	Date:.....
1st Primary cancer diagnosis & site	Dx:..... Site:.....
Date of second primary cancer diagnosis	Date:.....
2nd primary cancer diagnosis & site	Dx:..... Site:.....
Extent of disease Disease free Local disease present Recurrence of local disease Metastases & site	.... Site: .....
Date of local recurrence	.....
Date of metastases	.....
Treatment stage Pre-treatment On active treatment Monitoring Under investigation Post treatment assessment	....
Active Treatment Radiotherapy Chemotherapy	....

Data Definitions for Clinical data collection	
Date of 1st primary cancer diagnosis	Chart date cancer diagnosis was made from date on (in order of preference): pathology confirmation (for Lothian patients, use apex system), radiology reports eg CT scan report or from medical note annotations/letters. (For test reports, take date of test not date of report).

1st primary cancer diagnosis & site	Chart cancer diagnosis and site of primary lesion (obtain from medical notes as above)
Date of second primary cancer diagnosis	Chart date 2nd primary cancer diagnosis was made from date on (in order of preference): pathology confirmation (for Lothian patients, use apex system), radiology reports e.g. CT scan report or from medical note annotations/letters. (For test reports, take date of test not date of report).
2nd primary cancer diagnosis & site	Chart cancer diagnosis and site of 2nd primary lesion (obtain from medical notes as above)
Extent of disease Disease free Local disease present Recurrence of local disease Metastases & site	No disease evident (patient likely to be attending for routine follow-up for observation) Presence of disease – can be pre-treatment, or residual disease, i.e. disease still there after treatment Where patient has had previous confirmation of no evidence of disease after treatment/surgery but disease has re-appeared in the same site Presence of distant spread of disease (e.g. primary diagnosis is breast with metastases in spine). Chart also site(s) of metastases. (note that axillary node involvement with a breast cancer diagnosis is classed as local disease not metastatic whereas for most other cancers lymph node disease is metastatic – if in doubt ask a clinician for clarification i.e. Lucy/Dawn)
Date of local recurrence	Chart date local recurrence diagnosis was made from date on (in order of preference): pathology confirmation (for Lothian patients, use apex system), radiology reports e.g. CT scan report or from medical note annotations/letters. (For test reports, take date of test not date of report).
Date of metastases	Chart date metastatic diagnosis was made from date on (in order of preference): pathology confirmation (for Lothian patients, use apex system), radiology reports e.g. CT scan report or from medical note annotations/letters. (For test reports, take date of test not date of report).
Treatment stage Pre-treatment On active treatment Monitoring Under investigation (suspected relapse) Post treatment assessment	Diagnosis made but waiting for treatment (e.g. surgery, chemo, radiotherapy) Currently undergoing active anti-cancer treatment – radical or palliative (e.g. Surgery, radiotherapy or chemotherapy but also includes adjuvant Rx or chemo) Patient being seen for check-ups for basic monitoring/observation but not receiving any active treatment or under any investigation (may be on long-term hormone treatment e.g. Zoladex or Arimidex but not HRT) Where last medical entry suspects relapse, spread or new Cancer diagnosis and patient is waiting for investigations and/or results. (look for evidence in notes of raised tumour markers e.g. prostate- PSA, gynae - CEA125, teratoma - Alphafetaprotein, beta HcG) 1st appointment post treatment to determine new disease status and/or effect of treatment
Treatment Radiotherapy Chemotherapy	Note if currently receiving radiotherapy Note if currently receiving chemotherapy

PATIENT INFORMATION SHEET

EDINBURGH CANCER CENTRE SYMPTOM MANAGEMENT TRIAL

You are being invited to take part in a research trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information, take time to decide whether you wish to take part. Thank you for reading this.

What is the purpose of the Trial?

It is quite normal to suffer from some degree of stress symptoms in relation to the experience of having and being treated for cancer. Sometimes these symptoms are severe and may be called depression. We are testing a treatment for these symptoms and the best way to evaluate how effective this treatment is, is by testing it in a randomised clinical trial.

Randomised Clinical Trial:

In order to find out whether a new treatment is better than an existing one, we have to compare how much the patients improve with each treatment. In order for comparison to be a fair one, we cannot choose which patients have which treatment, rather they have to be randomly allocated (that is by chance) to one or other treatment.

In this trial, all patients will get the usual care for depression from their general practitioner and the Edinburgh Cancer Service. The aim of this trial is to see whether patients get better more quickly if they have the additional treatment as well.

What does the usual care for depression involve?

It is quite common for people who have cancer to suffer stress to some degree during their illness. General practitioners and doctors at the Edinburgh Cancer Centre are familiar with this. They may choose to let the stress take its course, to suggest that you try an "antidepressant" drug or refer you for some form of counselling. This is the usual care.

What does the additional treatment involve?

The patients who are allocated to the additional treatment will, as well as receiving usual care, also see a specially trained nurse. If you are allocated to this treatment, it will involve visiting the Cancer Research UK Building on the Western General site once a week for visits of 30-60 minutes for 6-8 weeks. In these sessions, you will talk with the nurse and discuss how to cope with stress.

What else will I be asked to do?

All patients who take part in the trial regardless of which group they are in will be asked to complete a number of questionnaires and to be briefly interviewed over the telephone by a member of the research team on two occasions (3 and 6 months after you have entered the study). These questionnaires will ask you questions about your physical and emotional symptoms and about what other treatments you have received.

What are the possible benefits of taking part?

The benefit of taking part is that your depression will be carefully monitored and we will review how you are at the end of the trial (6 months after you enter). If you are still depressed at that time, we will advise you and your doctor about further treatment. We do not know whether seeing the nurse for additional visits provides additional benefit; that is why we are doing the trial. The information we get from this trial will, we hope, help us to decide how best to treat patients in the future whose cancer is complicated by depression.

Why have I been chosen?
All patients attending the Edinburgh Cancer Centre are routinely asked about how they are feeling using a touch screen computerised questionnaire. The responses to these questionnaires are reviewed and patients with high scores are telephoned and asked additional questions. The answer to these questions tells us you have been severely stressed. You may therefore eligible to enter the trial.

Do I have to take part?
It is entirely up to you to decide whether you want to take part or not. If you do decide to take part, you will be asked to sign a consent form. Even if you decide to take part you are still free to withdraw from the study at anytime and do not have to give a reason for doing so. If you do decide not to take part or to withdraw this will not effect your future treatment from the NHS in any way.

What if something goes wrong?
Whilst it is very unlikely that you would be harmed by taking part in this research if you are there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this trial, the normal National Health Service complaints mechanisms should be available to you.

Is the information collected about me confidential?
All information collected about you during the course of this research will be kept strictly confidential within the research team. We would only pass on information to your doctors. Any information, which is presented elsewhere or published in medical journals, will be in a form so that you are not individually recognisable. It may be necessary for research regulatory authorities such as the Ethics Committee to have access to your medical notes to verify that our research findings are accurate but in such cases, your confidentiality will be preserved.

Who else would be involved?
Your own general practitioner and the cancer doctors at the Edinburgh Cancer Centre will be notified that you are participating in the trial.

Will I be paid?
You will not be paid for your participation but we will reimburse all reasonable travel expenses.

Who are the researchers?
If you have any further questions about the trial please contact Vanessa Strong the Trial Research Nurse on 0131 777 3525. The doctor in charge of the study is Dr Michael Sharpe, Consultant in Psychological Medicine at the Western General Hospital.

Can I get an independent opinion about this research?
If you wish to speak to a doctor who is knowledgeable about this sort of treatment but is independent of the trial you can contact Dr George Masterton, Consultant in Psychological Medicine at the Edinburgh Royal Infirmary on 0131 242 1398.

What do I do next?
Vanessa Strong will telephone you within the next few days to speak with you about this trial. Thank you very much for your help.

Study Number:
Patient identification Number for this trial:

CONSENT FORM

S M [a] R T -SYMPTOM MANAGEMENT RESEARCH TRIALS
Depression Trial

Researcher: Dr Michael Sharpe & Vanessa Strong

Please initial box

I confirm that I have read and understand the information sheet version ..... for the above study and have had the opportunity to ask questions. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. ☐

I understand my medical notes may be looked at by members of the research team or by individuals from regulatory bodies where it is relevant to the research. ☐

I agree to my GP being informed of my participation in this trial ☐

I agree to audio-recording of telephone interviews with researchers ☐

I agree to take part in the above study.

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Acknowledgements:

Professor Michael Sharpe (Supervisor); Dr Lucy Wall (second supervisor); Paul Currie; Louis Currie; Jordan Currie; Aileen Morton and the SMaRT Research Team.

Contribution to the Work in Each Chapter

Chapter 1: Background
I conducted the literature search and reviewed all the literature.

Chapter 2: A Nurse-Delivered Multiple Modality Approach to the Management of Major Depressive Disorder in Cancer Patients
I designed a multi-component cancer nurse delivered intervention collaboratively with Professor Michael Sharpe and tested it in a small non-randomised matched group design pilot study to perform a preliminary evaluation of its feasibility and efficacy in the treatment of MDD in cancer patients. I also delivered the intervention to all the patients in the pilot trial. I adapted the treatment manual from this pilot study and wrote the treatment manual and treatment delivery protocol for the randomised trial.

Chapter 3: Aims and Hypotheses
I created the hypotheses under the supervision of Professor Sharpe from which the trial methodology was developed.

Chapter 4: The Design of the Study
I developed the trial methodology collaboratively with Professor Sharpe and chose (and adapted) the outcome measures used in the trial. I also developed and wrote the trial protocol and submitted this for ethical approval. The depression screening system was conceived by Professor Sharpe and Dr Ann Cull and I developed this to provide the platform from which to identify patients with Major Depressive Disorder and set up and supervised this screening system in NHS practice. I designed and wrote all the staff training modules and training competency assessment protocols and delivered training to all trial team staff. I provided supervision collaboratively with Professor Sharpe for all trial staff in the screening of approximately 7,000 patients (for which there were approximately 25,000 screening events) as part of the screening service provided to the NHS and for the 200 patients within the trial. I supervised the conduct of the trial procedures including the clinical assessment of patients for Major Depressive Disorder and collaboratively with Professor Sharpe for Suicide Risk.

With regard to the actual treatment delivered, I developed and wrote a treatment guideline algorithm and a quality control manual and a treatment delivery compliance assessment tool and conducted all in-house treatment delivery adherence assessments. I also delivered the treatment to 20% of the trial patients and provided management of all 200 trial patients including liaison with the relevant health care professionals.
I was also responsible for and recorded and submitted all serious adverse events for trial patients. I collected all the medical information for all trial patients and conducted all the trial eligibility assessments and obtained trial consent.
With regard to the overall management of the trial, I organised all trial group meetings and wrote all trial reports.

Chapter 5: Analysis of Data and Statistical Power
I contributed (and debated the issues) to the analysis plan in multidisciplinary statistical plan meetings. The plan was finalised and written by the Trial Statistician, Rachel Waters. I developed the treatment compliance definition for the analysis.

Chapter 6: Trial Results
All primary and secondary analyses were conducted by the Trial Statistician. I interpreted the statistical data collaboratively with the Trial Statistician. I conducted all the analysis of the screening data supervised by Dr Carina Hibberd, Screening Data Manager.

Chapter 7: Exploration of Predictors of Outcome
Under the supervision of the Trial Statistician, I conducted the exploratory analyses. I interpreted the statistical data collaboratively with the Trial Statistician.

Chapter 8 to end: I wrote these chapters independently of any help.