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NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/70/05. The contractual start date was in September 2003. The draft report began editorial review in May 2008 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study

T Kendrick,[1] J Chatwin,[1*] C Dowrick,[2] A Tylee,[3] R Morriss,[4] R Peveler,[1] M Leese,[3] P McCrone,[3] T Harris,[5] M Moore,[1] R Byng,[6] G Brown,[5] S Barthel,[3] H Mander,[1] A Ring,[2] V Kelly,[3] V Wallace,[3] M Gabbay,[2] T Craig[5] and A Mann[3]

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Objectives: To determine (1) the effectiveness and cost-effectiveness of selective serotonin reuptake inhibitor (SSRI) treatment plus supportive care, versus supportive care alone, for mild to moderate depression in patients with somatic symptoms in primary care; and (2) the impact of the initial severity of depression on effectiveness and relative costs. To investigate the impact of demographic and social variables.
Design: The study was a parallel group, open-label, pragmatic randomised controlled trial.
Setting: The study took place in a UK primary care setting. Patients were referred by 177 GPs from 115 practices around three academic centres.
Participants: Patients diagnosed with new episodes of depression and potentially in need of treatment. In total, 602 patients were referred to the study team, of whom 220 were randomised.
Interventions: GPs were asked to provide supportive care to all participants in follow-up consultations 2, 4, 8 and 12 weeks after the baseline assessment, to prescribe an SSRI of their choice to patients in the SSRI plus supportive care arm and to continue treatment for at least 4 months after recovery. They could switch antidepressants during treatment if necessary. They were asked to refrain from prescribing an antidepressant to those in the supportive care alone arm during the first 12 weeks but could prescribe to these patients if treatment became necessary.
Main outcome measures: The primary outcome measure was Hamilton Depression Rating Scale (HDRS) score at 12-week follow-up. Secondary outcome measures were scores on HDRS at 26-week follow-up, Beck Depression Inventory, Medical Outcomes Study Short Form-36 (SF-36), Medical Interview Satisfaction Scale (MISS), modified Client Service Receipt Inventory and medical record data.
Results: SSRIs were received by 87% of patients in the SSRI plus supportive care arm and 20% in the supportive care alone arm. Longitudinal analyses demonstrated statistically significant differences in favour of the SSRI plus supportive care arm in terms of lower HDRS scores and higher scores on the SF-36 and MISS. Significant mean differences in HDRS score adjusted for baseline were found at both follow-up points when analysed separately but were relatively small. The numbers needed to treat for remission (to HDRS < 8) were 6 [95% confidence interval (CI) 4 to 26)] at 12 weeks and 6 (95% CI 3 to 31) at 26 weeks, and for

significant improvement (HDRS reduction ≥ 50%) were 7 (95% CI 4 to 83) and 5 (95% CI 3 to 13) respectively. Incremental cost-effectiveness ratios and cost-effectiveness planes suggested that adding an SSRI to supportive care was probably cost-effective. The cost-effectiveness acceptability curve for utility suggested that adding an SSRI to supportive care was cost-effective at the values of £20,000–£30,000 per quality-adjusted life-year. A poorer outcome on the HDRS was significantly related to greater severity at baseline, a higher physical symptom score and being unemployed.

Conclusions: Treatment with an SSRI plus supportive care is more effective than supportive care alone for patients with mild to moderate depression, at least for those with symptoms persisting for 8 weeks and an HRDS score of ≥ 12. The additional benefit is relatively small, and may be at least in part a placebo effect, but is probably cost-effective at the level used by the National Institute for Health and Clinical Excellence to make judgements about recommending treatments within the National Health Service. However, further research is required.

Trial registration: Current Controlled Trials ISRCTN84854789.

Contents

List of abbreviations

AHEAD	Assessing Health Economics Antidepressants Study
ARR	absolute risk reduction
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BP	bodily pain (SF-36 subscale)
BSI	Bradford Somatic Inventory
CBT	cognitive behavioural therapy
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CSRI	Client Service Receipt Inventory
DMEC	Data Monitoring and Ethics Committee
DSM-IV	*Diagnostic and Statistical Manual* (4th edition)
GH	general health (SF-36 subscale)
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
HTA	Health Technology Assessment
ICD-10	*International Classification of Diseases* (10th edition)
ICER	incremental cost-effectiveness ratio
LEDS	Life Events and Difficulties Schedule
MADRS	Montgomery–Åsberg Depression Rating Scale
MH	mental health (SF-36 subscale)
MISS	Medical Interview Satisfaction Scale
MREC	Multi-centre Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
PCT	primary care trust
PF	physical functioning (SF-36 subscale)
PHQ-9	Patient Health Questionnaire, 9-item version
PSAC	psychosocially active consultation
QALY	quality-adjusted life-year
R&D	research and development
RCGP	Royal College of General Practitioners
RE	role – emotional (SF-36 subscale)
RP	role – physical (SF-36 subscale)

continued

SD	standard deviation	SSRI	selective serotonin reuptake inhibitor
SF	social functioning (SF-36 subscale)	TSC	Trial Steering Committee
SF-36	Medical Outcomes Study Short Form 36-item questionnaire	VT	vitality (SF-36 subscale)

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Guidelines for the management of depression, including the National Institute for Health and Clinical Excellence (NICE) guidelines, recommend that antidepressants should not be used as first-line treatment for patients with depression below the severity threshold for major depressive disorder, yet general practitioners (GPs) in the UK frequently prescribe for such patients. Previous research on antidepressants has mostly been carried out in secondary care settings among patients with relatively severe depression, and there has been relatively little research on mild to moderate depression in primary care. Placebo-controlled trials have suggested that selective serotonin reuptake inhibitor (SSRI) antidepressants can be effective for mild depression, but it is not known if prescribing them is cost-effective in practice. We aimed to determine whether treatment with an SSRI antidepressant plus supportive care is more effective and cost-effective than supportive care alone. Secondary aims were to explore whether treatment is more effective for moderate than for mild depression and to explore patient factors which might predict a beneficial response to antidepressants.

Objectives

Our research objectives were:

1. To determine the effectiveness and cost-effectiveness of SSRI treatment plus supportive care, versus supportive care alone, for mild to moderate depression in patients with somatic symptoms in primary care.
2. To determine the impact of the initial severity of depression on the effectiveness and relative costs of these two approaches.
3. To carry out exploratory analyses of the impact on the effectiveness of these two approaches of demographic and social variables, including age, gender, employment status, life events and difficulties, the patient's self-reported duration of depressive symptoms, the patient's previous experience of antidepressant use, the number of physical symptoms, the patient's attribution of his or her symptoms (physical cause versus non-physical cause) and alcohol consumption.

Methods

Design

The study was a parallel group, open-label, pragmatic randomised controlled trial.

Setting

The study took place in a UK primary care setting: 212 general practices around three academic centres (in Southampton, Liverpool and London) agreed initially to take part. Patients were referred by 177 GPs from 115 practices.

Participants

Patients diagnosed with new episodes of depression by the GP and potentially in need of treatment were referred to the study team. Both the patients and their GPs had to be in equipoise about the need for antidepressant treatment and prepared for the patient to be randomised to being prescribed an SSRI. Inclusion criteria were age 18 or over, symptoms for at least 8 weeks, no antidepressant treatment within the previous 12 months, no current receipt of counselling or psychological therapies, a score of between 12 and 19 on the 17-item Hamilton Depression Rating Scale (HDRS) and at least one physical symptom on the Bradford Somatic Inventory (BSI). Exclusion criteria were a lack of the spoken or written language skills necessary to take part, expressed suicidal intent, reported significant substance misuse and a score of 13 or more on the Alcohol Use Disorders Identification Test (AUDIT) questionnaire. In total, 602 patients were referred to the study team, of whom 220 were randomised into the study.

Interventions

All treatments were delivered by the patients' GPs, reflecting usual practice in the UK. They were asked to provide supportive care to all participants in follow-up consultations 2, 4, 8 and 12 weeks

after the baseline assessment. They were not asked to provide any specific interventions in the follow-up consultations in the supportive care alone arm, but were asked to prescribe an SSRI antidepressant of their choice to those patients in the SSRI plus supportive care arm and to continue treatment for at least 4 months after recovery, in line with guidelines. They could switch antidepressants during treatment if they deemed this to be necessary. They were asked to refrain from prescribing an antidepressant to those randomised to the supportive care alone arm during the initial 12-week treatment period, but could use their judgement to prescribe antidepressants to patients in that arm if they became more depressed and in need of treatment.

Outcome measures

The primary outcome measure was the score on the HDRS at 12-week follow-up. Secondary outcome measures were the HDRS at 26-week follow-up and scores on the Beck Depression Inventory (BDI), Medical Outcomes Study Short Form 36-item (SF-36) questionnaire measure of generic health status, Medical Interview Satisfaction Scale (MISS), modified Client Service Receipt Inventory (CSRI) patient questionnaire for use of health and social services and informal care, and GP medical record data for primary care contacts and drug prescriptions. Inter-rater reliability on the HDRS between researchers in the three centres was checked at four points during recruitment and was found to be high.

Analysis

The primary analysis was by intention to treat using double-sided significance tests. We used analysis of covariance, controlling for baseline value and recruitment site and allowing for clustering by GP, to estimate treatment effectiveness using the HDRS at both follow-ups independently. Longitudinal analysis was also performed, in which 12-week and 26-week outcomes were modelled simultaneously, and both time point and time point × treatment interaction effects were tested in these models. Baseline predictors of a lack of follow-up data were identified by means of logistic regression and the models of predictors of outcomes were refitted to include these variables. Cost-effectiveness was expressed in terms of incremental cost-effectiveness and cost–utility ratios. In addition, cost-effectiveness acceptability curves (CEACs) were generated, synthesising data on costs and outcomes, for varying levels of acceptability of costs.

Results

More than 90% of patients in each arm received supportive care from the GPs, with a mean number of consultations of around four during the 12-week treatment period. Selective serotonin reuptake inhibitor antidepressants were received by 87% of patients in the SSRI plus supportive care arm and also by 20% of patients in the supportive care alone arm. Longitudinal analyses demonstrated statistically significant differences in favour of the SSRI plus supportive care arm in terms of lower HDRS scores, higher scores on the SF-36 mental health subscale and higher scores on the MISS, but not in terms of lower BDI scores. Differences in the SF-36 vitality score were of borderline significance, and the other SF-36 subscales were not significantly different. Significant mean differences in HDRS score adjusted for baseline were found at both follow-up points when analysed separately, but were relatively small: 2.3 points at 12 weeks and 1.7 points at 26 weeks. The numbers needed to treat (NNTs) for remission (to HDRS < 8) were 6 [95% confidence interval (CI) 4 to 26) at 12 weeks and 6 (95% CI 3 to 31) at 26 weeks, and the NNTs for significant improvement (HDRS reduction $\geq 50\%$) were 7 (95% CI 4 to 83) and 5 (95% CI 3 to 13) respectively. Costs were slightly higher in the SSRI plus supportive care arm, but were not significantly different. Incremental cost-effectiveness ratios and cost-effectiveness planes suggested that adding an SSRI to supportive care was probably cost-effective, with mean costs of £90 per point improvement on the HDRS, and £14,854 per quality-adjusted life-year (QALY) gain. The CEAC for utility suggested that adding an SSRI to supportive care was cost-effective at the values of £20,000–£30,000 per QALY used by NICE, with a 65–75% probability. A poorer outcome on the HDRS was significantly related to greater severity at baseline, a higher physical symptom score and being unemployed. The effect size of unemployment was of similar magnitude to that of treatment. None of the other possible predictors was significantly related to outcome or response to treatment. Further analyses are planned of possible relationships between life events and remission, the nature of supportive care received, patterns of change in depressive symptoms and the components of patient satisfaction.

Conclusions

Treatment with an SSRI plus supportive care is more effective than supportive care alone for patients with mild to moderate depression in

primary care in the UK, at least for those with symptoms persisting for 8 weeks and with a score of ≥ 12 on the HDRS, equivalent to around 12 on the Patient Health Questionnaire, 9-item version (PHQ-9) and 9 on the Hospital Anxiety and Depression Scale, depression subscale (HADS-D). The additional benefit is relatively small, and may be at least in part a placebo effect, but is probably cost-effective at the level used by NICE to make judgements about recommending treatments within the National Health Service (NHS).

Implications for further research

In order of priority, these are as follows:

- More studies of drug and non-drug treatments for mild depression in primary care are needed, as the evidence base for the treatment of mild depression is still relatively small.
- More research is required on the natural history of mild to moderate depression and predictors of chronicity because, although many patients recover within weeks without treatment, a significant number do not improve over 6 months of follow-up.
- More trials of antidepressant treatment are needed among patients with persistent and/or repeated mild depression, in mild depression in the context of a history of severe depression, in the context of physical illness and in patients over the age of 70 years. There are reasons to believe that antidepressants may be a relatively good or bad idea in these subgroups, rather than to take the blanket view that antidepressants should always be second-line treatments for mild depression (as suggested by NICE). We also know relatively little about the required doses of antidepressants and duration of treatment in these groups.
- More research is needed to identify the most effective elements of supportive care.
- More research is required into the differences between the HDRS, BDI and other measures of depression, to explore whether they measure different aspects of depression and differ in sensitivity to change in relation to drug, psychological and other treatments.
- More economic evaluations are required and the appropriateness of the methods used to generate QALYs should be assessed.
- Better measures of outcome for depression studies, including patient-derived measures, need to be developed.

Trial registration

This trial is registered as ISRCTN84854789.

Chapter 1
Introduction

Depression is a very common and costly condition, both in terms of the personal suffering of those it affects, and in terms of the costs to the nation through absence from work and treatment costs. Most of the treatment of depression takes place in primary care, which in the UK means general practice, rather than in the secondary care setting of specialised psychiatric practice. The most common general practice treatment for depression is the prescription of antidepressant drugs, and there is a clear need for good research evidence on the cost-effectiveness of these drug treatments to inform decisions about treating patients.

The increasing use of antidepressants in general practice

Antidepressant prescribing rates in the UK have been rising year on year since the early 1990s. This is costly and may not be appropriate. Expenditure on antidepressants in England rose from £147 million to £279 million between 1995 and 1998, with the bulk of the increase being due to increased prescribing in general practice.[1] Prescribing of antidepressants has continued to increase annually since the turn of the century. The National Health Service (NHS) Prescription Pricing Authority reported a 36% increase between 2000 and 2005, to 7.3 million items, costing £91 million, in the quarter to June 2005 (www.nhsbsa.nhs.uk/PrescriptionServices/Documents/PrescriptionServices/imPACTjan2006.pdf). Prescription numbers have continued to rise since then, to more than 9.6 million items in the last quarter of 2007 (Alison Bowes, Prescription Analysis Service, NHSBSA Prescription Pricing Division, personal communication).

The Defeat Depression Campaign, mounted by the Royal Colleges of Psychiatrists and General Practitioners in the 1990s, was a promotional campaign designed specifically to increase both doctor and patient awareness of depressive disorders.[2] The message has been caricatured as 'see more, treat more'[3] and was probably part of the reason for the increase in antidepressant prescribing in general practice starting in the early 1990s. Another likely reason was the introduction of the selective serotonin reuptake inhibitors (SSRIs), starting with fluoxetine in 1990, as they were perceived to be better tolerated by patients than the older tricyclic antidepressants.[4] However, much of this increased prescribing probably falls outside current guideline recommendations and may not be appropriate. This is because antidepressants are frequently being prescribed for relatively mild depression, for which they are not recommended in the guidelines. Guidelines recommend drug treatment only for 'major depression' of a minimum level of severity.

Depression and its classification

Depressive symptoms range along a continuous spectrum from everyday sadness to suicidal ideas, and any cut-off between 'normal' and 'depressed' patients is, to an extent, arbitrary, but categorical classifications are necessary in order to make decisions about intervening in clinical practice. Depression is classified in two ways: categorically, in descriptive diagnostic classification systems; and dimensionally, in terms of scores on continuous self-rating questionnaire measures.

Categorical classification

Major depression

According to antidepressant treatment guidelines, the category of 'major depression' predicts the need for active treatment, irrespective of environmental factors except for bereavement.[5] The World Health Organization's *International Classification of Diseases*, 10th edition (ICD-10) criteria for major depressive disorder state that at least five of nine symptoms (depressed mood, loss of interest or pleasure in activities, weight change, change in sleep pattern, agitation or retardation, fatigue, feelings of worthlessness or guilt, impaired concentration and suicidal thoughts) must be present most of the day, nearly daily, for a minimum of 2 weeks, accompanied by significant impairment of functioning.[6] The American Psychiatric Association's *Diagnostic and Statistical*

Manual, 4th edition (DSM-IV) classification of major depression also requires five out of nine symptoms, one of which must be depressed mood or loss of interest and pleasure in usual activities.[7]

The World Health Organization's multicountry survey of 2000–1 found that major depression affected around 5% of women and 3% of men per year.[8] Major depression was identified as the fourth leading cause of global health burden among all diseases, responsible for 4.4% of total disability-adjusted life-years lost on average,[8] and is predicted to be second after ischaemic heart disease by 2020.[9]

'Mild depression', 'minor depression' and 'dysthymia'

In addition to the 3–5% of people with major depression, three to four times as many have depressive symptoms below the cut-off for the diagnosis. In UK general practice, roughly 5% of attenders are found to be suffering from major depression, 5% from mild depression and around 15% from some depressive symptoms.[10] Mild (or 'minor') depression is diagnosed if low mood or loss of pleasure is accompanied by up to three other symptoms of depression.[11] Dysthymia is mild depression which has persisted for 2 years or more. Despite its name, mild depression and dysthymia can be associated with significant distress and impairment of social functioning,[12,13] and overall depression of all levels of severity is the second- (for women) or third- (for men) biggest cause of long-term sickness certification in the UK.[14] It is therefore not surprising that general practitioners (GPs) frequently decide to prescribe antidepressants for patients with mild depression, but the routine treatment of mild depression is not recommended in the guidelines.

The threshold for drug treatment

In common with other depression guidelines, the UK's National Institute for Health and Clinical Excellence (NICE) clinical guidelines for the management of depression recommend antidepressant medication as first-line treatment for depression in primary care only for major depression, with at least five of the symptoms as listed above, and of at least moderate severity in terms of impairment of functioning.[5,11] The NICE guidelines recommend that antidepressants should not normally be prescribed for mild depression, which is defined in terms of a maximum of four symptoms, although it should not be ignored, but should be monitored for a period of 2 weeks or more ('watchful waiting'), in case the patient goes on to develop more severe symptoms.[11] During this period, a variety of self-help measures are recommended, including advice on sleep hygiene and anxiety management, regular exercise, and the provision of books ('bibliotherapy') or interactive computer programs based on the principles of cognitive–behavioural therapy (computerised CBT),[15] which encourage patients to identify and tackle their depressive thoughts, and to become more active.

Despite the guideline recommendations, however, antidepressants are frequently prescribed for depressive symptoms below the threshold for major depression, perhaps as a result of the perceived pressure to treat more patients, in the context of a severe lack of availability of alternative treatments, particularly psychological therapies.[16–18] Another reason is that the recommendations on the threshold for treatment are not supported by a great deal of good research evidence. Previous research on antidepressant treatment has mostly been carried out in secondary, specialist care settings, with patients with relatively severe depression, and there has been comparatively little research in primary care on patients with mild depression to guide GPs on the threshold at which antidepressants should be offered.

Previous research on the treatment threshold

Several placebo-controlled trials have been conducted to determine the efficacy of antidepressants in treating depression in primary care. These trials often classify the patients they include in terms of the DSM or ICD diagnostic systems, but they tend to measure outcome using continuous measures of depressive symptoms, rather than the more descriptive DSM and ICD classifications. The outcome measure most commonly used is the Hamilton Depression Rating Scale (HDRS).[19]

Major depression

A general practice-based placebo-controlled trial of the tricyclic antidepressant amitriptyline found that patients with 'probable major depressive disorder' benefited from drug treatment, but those with 'minor depression' did no better on the antidepressant than on placebo.[20] These findings resulted from a post hoc subgroup analysis dividing the patients into those who did or did not fulfil

research diagnostic criteria for a diagnosis of probable major depression, and the study was not set up a priori specifically to assess the relationship between severity and response to treatment. In this study, patients with 'probable major depression' had HDRS scores ranging from 16 to 19 and those in the 'minor depression' category had HDRS scores of 12–15. Despite the fact that this analysis was post hoc, the threshold of 'major depression' formed the basis for early guidelines on drug treatment.[10]

Supportive evidence for the usefulness of the category of major depression as a treatment threshold also came from two other studies which were not randomised controlled trials of drug treatment. One was a US trial of collaborative management to achieve greater adherence to guidelines[21] and the other was a UK trial of nurse intervention to improve compliance with antidepressants.[22] Both studies found that outcome was improved only among patients with major depression, although, again, these were post hoc subgroup analyses, and these studies were not set up to assess the relationship between severity and response to treatment. A subsequent systematic review and meta-analysis of 15 trials, mostly of tricyclic antidepressants, confirmed modest benefit from drug treatment over placebo for major depression in primary care.[23]

Mild depression

A placebo-controlled trial of the SSRI paroxetine, versus problem solving, versus watchful waiting, for mild depression in a primary care population, was undertaken in the US.[24] Patients were selected on the basis of diagnostic criteria for minor depression or dysthymia, and an HDRS score of at least 10. The results were mixed: among patients aged 18–59 years with dysthymia, paroxetine improved remission (to a score of 6 or less on the HDRS) at 11 weeks follow-up compared with placebo plus non-specific clinical management, while for minor depression the two treatments were equally effective.[25] Among patients aged 60 and over, paroxetine was beneficial in dysthymia and among more severely impaired patients with minor depression.[26] This study suggested that 'watchful waiting', i.e. supportive care but without the prescription of antidepressants, might be an appropriate treatment option for minor depression, at least in adults and elderly patients with mild impairment.

This study also supported the use of antidepressants for dysthymia, suggesting that a longer duration of depression may be an important predictor of likely benefit from treatment. A previous systematic review and meta-analysis of secondary care studies had suggested that antidepressant drug treatment was effective in the management of dysthymia, although most of the research studies analysed were of relatively poor quality.[27]

A randomised placebo-controlled trial of fluoxetine carried out among 162 patients with 'minor depressive disorder' found that fluoxetine was better in terms of clinical effectiveness when measured using the HDRS.[28] However, the mean difference between intervention and control groups at follow-up was only 1 point on the HDRS scale, and it is debatable whether such a small difference is clinically significant.[29] In addition, one-third of the patients had a past history of major depressive disorder, and their HDRS scores at baseline ranged from 6 to 21 on the 17-item scale, which means they included people with major depression as well as those with mild depression.[29,30]

Most recently, a study of the newer dual-action serotonin and noradrenaline reuptake inhibitor duloxetine found that it was more effective than placebo in 159 patients with 'milder major depressive disorder' (scores on the HDRS between 15 and 18).[31] The mean difference was 2.9 points on the HDRS, which is more significant clinically, but it should be noted that this study was a post hoc subgroup analysis of pooled data from two trials.

Predictors of response to treatment

Adverse life events and difficulties

The placebo-controlled trial of amitriptyline in general practice referred to above found no difference between those categorised as having endogenous and those having non-endogenous (or 'reactive') depression. The authors recommended drug treatment for major depression, regardless of demographic characteristics, a past history of depression or the presence or absence of endogenous features.[20] These findings led to the guideline recommendations to prescribe drug treatment for depression if symptoms are severe enough and functioning is impaired, even if there seems to be an understandable cause for depression such as adverse events or continuing difficulties in the patient's life (apart from bereavement).[20,20,32,33]

However, the importance of social factors in depression is undeniable, and there is substantial evidence to suggest that both onset and recovery are related to life events and difficulties. Depression is strongly associated with lower socioeconomic status,[34,35] poverty,[36] unemployment,[35,37] separation or divorce[34,38] and poor housing.[39] Predisposing factors among women include demanding child care,[40] lone motherhood and poor social support.[41]

Adverse events have been shown to lead to depression by research using the Life Events and Difficulties Schedule (LEDS).[41,42] A lower severity of premorbid life difficulties has also been shown to be associated with a reduced time to remission, at least among patients with high self-esteem and better coping strategies.[43] Recovery from depression is related to positive social support and life events which can be perceived as 'fresh starts', which may or may not be related to the original adverse events and difficulties associated with onset.[44] A reduction in marked social difficulties has been found to predict recovery from depression among patients in primary care,[45] whereas recognition and drug treatment by the general practitioner has not.[46,47]

Currently, there is a limited evidence base to guide treatment choices for individual patients in primary care. Preliminary analysis of data from the Outcomes of Depression International Network (ODIN) study of problem-solving therapy versus group psychoeducation[48] showed that recent adverse life events had an adverse effect on outcome for women, but not for men. The outcome was also worse with increasing duration of depression prior to baseline assessment, but no different between episodes which were reported as first or recurrent. Contact with the GP and use of antidepressants were not related to outcome. These results may not apply, however, to patients randomised to drug treatment.

Research into psychosocial predictors of response carried out in secondary care suggested that greater emotional support and a relative lack of experience of adversity, particularly in domains of the patient's life invested with greater commitment, were more strongly related to recovery than was drug treatment.[49] As findings in secondary care may not generalise to primary care, however, it remains uncertain whether such social factors would predict response to drug treatment in a primary care setting.

Comorbid physical disorder

Another possible predictor of response to antidepressant treatment is comorbid physical disorder. This may be especially important in primary care, where depressed patients often present with somatic symptoms.[50,51] In general, somatic presentations of depressive disorder are associated with a lower severity of depressive symptoms but similar impairments in function and a similar prognosis.[52] However, depression is less likely to be diagnosed in the presence of physical symptoms or physical illness.[50] Little is known about whether comorbid physical illness affects the response to antidepressant treatment because patients with comorbid illness are often excluded from trials.[53] Patients with alcohol misuse are also often excluded too, yet primary care practitioners frequently have to decide whether or not to treat depression in someone with significant alcohol use.

Research in secondary care settings suggests that antidepressants can work for patients with coexisting medical illnesses.[54] Evidence about the effectiveness of antidepressants for patients presenting with pain or other somatic symptoms, which is very common in primary care, is mixed.[55] A distinction needs to be drawn between somatic symptoms, which may be caused by physical illness and just happen to coincide with depression on the one hand, and somatic presentation of underlying mental disorder ('somatisation') on the other.[56] Illness beliefs are important and are related to outcome. Reattribution for somatised mental disorder was found to lead to recovery in patients with minor depression and to improved function in those with partly psychologising attributions, but not in patients with totally somatising attributions where improvements were confined only to major depression.[57]

The need for a new study

A new study was needed for several reasons. First, we considered that the findings from the US that SSRIs may benefit some patients with 'minor' depression or dysthymia[25] might not generalise to primary care in the UK, as the type of supportive care usually provided in the UK may differ in quality or quantity from the 'watchful waiting' provided in the US study.

Second, we considered that, even if SSRI treatment is efficacious compared with placebo in mild

depression, its effectiveness and cost-effectiveness in practice need to be established. All the studies referred to above were placebo-controlled studies aimed at determining the efficacy of antidepressants. To establish effectiveness and cost-effectiveness, a pragmatic open-label trial is necessary, comparing active drug treatment plus supportive care with supportive care without prescription of a drug, as opposed to a placebo-controlled trial, as placebos are not used in practice and cannot be costed as part of usual health care. Cost-effectiveness also needed to be established within the UK health-care system, which is quite different from the US system. For example, GPs in the UK act as gatekeepers to secondary care, whereas in the US patients commonly self-refer to specialists.

Third, another issue that needed to be addressed was whether predictors of response to antidepressant treatment could be identified, to help GPs decide which patients should be offered such treatment. Important predictors to include were sociodemographic factors, the presence of recent adverse life events and ongoing life difficulties, the duration of depression, previous depression and previous experience of using antidepressants, the presence of somatic symptoms, symptom attribution to a physical cause rather than a psychological cause and level of alcohol use.

Our research questions were, therefore:

1. Is treatment with an SSRI plus supportive care more effective and cost-effective than supportive care alone?
2. If it is more effective, does this apply across the whole range of severity of symptoms of mild to moderate depression?
3. What patient factors might predict the need for antidepressant treatment and a beneficial response?

To answer these questions, we designed a randomised controlled trial of SSRI treatment plus supportive care versus supportive care alone, measuring a number of possible predictors of response.

Objectives and hypothesis

The research objectives were:

1. To determine the clinical effectiveness and cost-effectiveness of SSRI treatment plus supportive care versus supportive care alone, for mild to moderate depression in patients with somatic symptoms in primary care. Our first hypothesis was that SSRI treatment plus supportive care would be more effective and cost-effective than supportive care alone.
2. To determine the impact of the initial severity of depression on the effectiveness and relative costs of these two approaches. Our second hypothesis was that SSRI treatment plus supportive care would be relatively more effective and cost-effective than supportive care alone among patients scoring 16–19 on the HDRS, compared with those scoring 12–15.
3. To carry out exploratory analyses of the impact of the following factors on the effectiveness of these two approaches:
   i. demographic and social variables including age, gender, and employment status
   ii. life events and difficulties
   iii. the patient's self-reported duration of depressive symptoms
   iv. the patient's previous experience of antidepressant use
   v. the number of physical symptoms
   vi. the patient's self-rating of the cause of his or her illness (physical versus psychological)
   vii. alcohol consumption.

Chapter 2
Methods

Trial design

The study design was a randomised controlled trial comparing treatment by means of an SSRI plus GP supportive care with GP supportive care alone, over 26 weeks of follow-up. The aim was to establish the clinical effectiveness and cost-effectiveness of SSRI antidepressants prescribed by the GP over and above supportive care (defined below) in normal clinical practice conditions.

Setting

Patients were recruited in general practice surgeries around three academic centres: the University of Southampton; the University of Liverpool; and the Institute of Psychiatry, King's College London.

Ethical approval and Primary Care Trust Research Management and Governance approval

Ethical approval was awarded by the West Midlands Multi-Centre Research Committee (MREC): reference number 02/7/091. Research Management and Governance approval was obtained from 57 primary care trusts (PCTs) during the course of the study: 21 around Southampton, 27 around Liverpool and nine around London.

Practice and general practitioner recruitment

Initially, practices in each centre known to the research teams from previous research studies were approached and asked to take part. However, only a small proportion of practices approached were willing to participate. It soon became apparent, therefore, that referrals from these practices would be insufficient to meet the required target, so all practices in neighbouring PCTs were systematically approached with a letter which had been previously approved by the MREC (see Appendix 1). This was then followed up with a telephone call to the practice manager to ascertain any interest in participating among the GPs within each practice. Where the response was positive, one or more members of the research team (including one of the medical team members where possible) arranged to visit the practice to explain the study in detail and to answer questions about it. Interested GPs were informed verbally and in writing of the patient inclusion and exclusion criteria (see Appendix 2), how to refer patients into the study, the consent procedure involving both the GPs and the researchers, the randomisation procedure and the details of interventions to be offered in each arm of the trial.

No financial incentive was offered to the GPs for taking part but they were advised that they would be reimbursed for their involvement at the rate of £49 per patient referred to the study. This money was provided through the ad hoc NHS Research and Development (R&D) funding arrangement for service support costs, and was calculated to cover the cost of an extra hour of GP time for referring and monitoring study patients, based on the prevailing cost of employing locum tenens doctors at the rate of £45 per hour, plus 20 minutes of clerical time based on the prevailing average rate of £12 per hour.

Over the 41 months during which patients were recruited, various strategies were adopted to keep the study in the GPs' minds when seeing potential participants in their surgeries. They included sending emails about the study approximately once a month; visiting them face to face whenever possible and appropriate; sending quarterly study newsletters by both post and email; sending Christmas cards; delivering desktop reminders in the form of THREAD-branded computer screen stickers (furry worms) and notepads; and sending letters at intervals, pointing out items on depression in the popular or medical press. The researchers also attempted to make contact with the GPs when visiting the surgery to collect medical record data after participating patients had completed the study, and took the opportunity to request further referrals.

Clinical support officers of the Mental Health Research Network were also helpful in contacting

practices to promote the study, particularly in the London and Liverpool centres.

Patient recruitment

Inclusion criteria

Patients were eligible for inclusion if:

- they were aged 18 and above
- they were diagnosed as depressed by their GP
- they were potentially in need of treatment
- they had had symptoms for at least 8 weeks
- they had received no antidepressant treatment within the previous 12 months
- they were not in receipt of counselling or psychological therapies at baseline
- they agreed to discuss, with the research team, being allocated either to antidepressant treatment plus support from their GP or to GP support without drug treatment
- at the baseline assessment, they scored between 12 and 19 on the HDRS[19] (see below)
- at the baseline assessment, they had at least one symptom on the Bradford Somatic Inventory (BSI).[51]

It was stressed to the GPs that we were asking for patients to be referred into the study who had been diagnosed as depressed in the course of their usual consultations. We did not ask them to identify, by searching their practice records, patients who had been previously diagnosed, as we wanted only incident cases of depression where no antidepressant treatment had already been tried, rather than prevalent cases who had already had treatment, so they must not have received drug treatment for depression within the previous 12 months. This exclusion criterion was designed to limit the sample to patients presenting with new bouts of depression, as we aimed to determine the effectiveness and cost-effectiveness in new episodes and wanted to be clear we were not dealing with relapsing or chronic depression. To avoid including patients with more transient depression, for whom treatment might be unnecessary, patients needed to have had symptoms for at least 8 weeks. They also had to have at least one somatic symptom, as the Health Technology Assessment (HTA) commissioning brief for the study was the treatment of depression in patients with somatic symptoms.

We asked for referral of only those patients for whom the likely benefit of treatment was uncertain in the mind of the GP, as it was essential that the GP was in equipoise about the likely outcome. In addition, we asked for only those patients who were themselves in reasonable equipoise about the need for treatment, such that they would be prepared to be allocated to drug treatment or no drug treatment by the allocation process.

Exclusion criteria

Patients were excluded from the study if:

- they did not have the spoken or written language skills necessary to take part
- they expressed suicidal intent
- at the baseline assessment, they were found to have HDRS scores of less than 12 or greater than 19
- at the baseline assessment, they reported significant substance misuse, determined by screening questions (this was an addition to the original protocol)
- at the baseline assessment, they scored more than 12 on the Alcohol Use Disorders Identification Test (AUDIT) questionnaire (this was an addition to the original protocol, see below).[58]

The GPs were advised that patients expressing suicidal intent, and those scoring above 19 on the HDRS, would be considered to be suffering from severe depression and would therefore be ineligible for randomisation to treatments designed for mild to moderate depression. Those with scores of less than 12 were considered to be suffering from subthreshold symptoms, for which possible randomisation to drug treatment would be inappropriate given the risks of adverse effects. Patients with significant substance or alcohol misuse were excluded because of the risk of adverse interactions with antidepressants.

Patient consent

The task of referral of patients into the study was kept as simple as possible for the participating GPs, who were asked only to give a brief verbal explanation of the study to eligible patients and to obtain their consent for the research team to contact them. In the original proposal, only verbal consent was envisaged, but early in the course of the study, in July 2004, it was decided to change this to written consent, as some of the referring GPs were not happy to pass on patient details without such consent. The change was approved by the MREC and a form (see Appendix 3) was

provided to the GPs to use for this purpose. The form was sent by fax to the research team, who then contacted the patient to arrange a visit to explain in detail what the study involved, prior to obtaining informed consent to take part. The patient was given a study information sheet (see Appendix 4) by the referring GP to read before the first visit from the researcher, which was usually within a few days of referral into the study, at which point the researcher dealt with any questions the patient had about the study. The patient was then given a further week to consider whether or not they wanted to take part and if they were happy to do so, the researcher returned to obtain written consent (see Appendix 5), before establishing the patient's eligibility for the study and conducting the baseline assessment. This procedure, involving two researcher visits to obtain consent, was stipulated by the MREC, in order to give potential participants at least a week to consider joining the study.

In the original design, referred patients were given only two choices when asked for their written consent to participate: 'yes' or 'no'. However, it was apparent early in the study that some patients remained undecided about taking part despite having had more than a week to consider it. Under the terms of the original protocol they were forced to make a decision at that point, and the default for those still undecided was to decline. As a relatively large number of possible participants who accepted referral to the study subsequently declined to take part at the point of obtaining written consent (see Chapter 4), it was decided, in July 2004, to give them a third option in order not to lose those who needed longer to decide whether or not to take part. In addition to an immediate 'yes' or 'no', they were offered a third option of 'undecided' which, it was explained, meant that they could be approached again 4 weeks later to reconsider participation. This change was approved by the MREC (see Appendix 6).

Piloting of partial patient preference design

Another strategy designed to tackle the issue of the large number of potential participants referred to the study who subsequently declined to take part was suggested by the Chair of the Data Monitoring and Ethics Committee (DMEC), Professor Michael King. He pointed out that a considerable number of patients declared that the reason they declined was because they could not accept possible randomisation to antidepressant drug treatment. He suggested adding a third, patient preference arm, in which patients could take part but have the treatment of their choice. Early in the course of the study, in December 2004, approval was gained from both the sponsor and the MREC to pilot a partial preference design. This was piloted in two of the three centres (Southampton and Liverpool) between January and April 2005. At the end of the pilot, the results were reviewed by the Study Group and Trial Steering Committee (TSC), and it was agreed not to change over to a partial preference design, as it was apparent that, while the total number of patients referred into the study did not increase significantly during the pilot, some patients who would have been prepared to be randomised had the choice of treatment not been offered, were deciding to enter the preference arm instead. So, although more patients in total could have been enrolled into the study by including a preference arm, this would have been at the expense of reduced numbers in the two randomised arms. The results of the partial preference pilot are shown in Chapter 4.

Randomisation and concealment of allocation

Block randomisation with random block sizes, stratified by severity subgroup (HDRS scores 12–15 and 16–19 respectively) and by recruiting centre, was carried out independently of the research team by the Institute of Psychiatry Mental Health and Neuroscience Clinical Trials Unit. Following completion of the baseline assessment, if the patient was eligible for randomisation, the researcher faxed the patient's details to the study co-ordinator, who either emailed or telephoned the remote randomisation service. The study co-ordinator then faxed the allocation details to the GP (see Appendix 7) and informed the patient by telephone. If the patient was unsuitable, the GP received a fax explaining why the patient was not able to be entered into the study (see Appendix 8). The researcher who had visited and carried out the baseline assessment, therefore, remained blind to the treatment allocation. Wherever possible, the researchers were kept blind to the treatment arm while carrying out the follow-up interviews. Participating patients were asked, when contacted prior to the follow-up interviews, not to reveal whether or not they had been prescribed antidepressants. All instances where researchers became aware of the patient's allocation to treatment arm were recorded.

Interventions

GP supportive care alone

The GPs were asked to arrange to see and provide support to the patients randomised to supportive care alone in follow-up consultations 2, 4, 8 and 12 weeks after the baseline assessment. They were not asked to provide any specific intervention during their consultations but were asked to refrain from prescribing antidepressants during this 12-week period. However, if the patients' depression worsened during the 12 weeks and the GPs felt that they were in need of antidepressants then they were advised that they could initiate drug treatment. If this did occur, then the patients remained in the study and were followed up as planned, in the supportive care alone arm, on an intention-to-treat basis.

SSRI antidepressant plus GP supportive care

The GPs were asked to prescribe an SSRI antidepressant of their choice to those patients randomised to the drug arm of the trial, and to arrange to see them in consultations 2, 4, 8 and 12 weeks after randomisation, as above. In the original proposal, fluoxetine was identified as the drug of choice for the study, but it became apparent early in the recruitment of GPs, by July 2004, that restricting them to prescribing only one SSRI would preclude many of them from taking part. Therefore, the choice of antidepressant was extended to include all currently used SSRIs (fluvoxamine, sertraline, paroxetine, citalopram and escitalopram) rather than just fluoxetine. The GPs were also advised that they could switch antidepressants should the first choice prove unsuitable for the patient; initially switching to another SSRI if possible, but switching to a different class if that became necessary. The GPs were advised to continue treatment for 4 months after recovery (in line with antidepressant guidelines), but it was stressed to them that this was a pragmatic study, meant to be as close as possible to usual practice, and that they should use their clinical judgement in relation to the duration of treatment, in discussion with the patient.

Other treatments

After completion of the baseline assessment and randomisation, the GPs were free to refer patients in either arm for counselling, psychological therapy, exercise schemes, or other interventions for depression if this was appropriate in their judgement, but waiting times for counselling and psychological treatment were such that patients would not usually receive this before the 12-week follow-up assessment. All treatments received were recorded (see section on use of services, below).

Patient assessments

The baseline assessment took place immediately after consent was obtained from the patient and follow-up interviews were carried out as close as possible to dates 12 and 26 weeks after randomisation. After 26 weeks, whether or not the patient had been assessed in follow-up interviews as planned, the researcher visited the patient's practice and extracted data from their medical records, on health service contacts (including practice, community, and hospital contacts with GPs, nurses, hospital staff and community mental health professionals) and treatments received, including numbers of antidepressants prescribed. *Figure 1* shows the flow of patients through the study.

Outcome measures

Depressive symptoms

The primary outcome measure was the score on the17-item HDRS at 12 weeks (see Appendix 9).[19] A large number of studies have shown the HDRS to be a valid and reliable measure of depression,[59] and it has been shown to be sensitive to changes in response to drug treatment in a general practice setting.[60] All the researchers involved in assessing patients using the HDRS received extensive initial and follow-up training in the measure.[30]

Initial training was carried out by a psychiatrist with long-standing experience of training investigators in the use of the HDRS for the purposes of clinical research, Dr David Baldwin of the Mental Health Group at the University of Southampton. Training included the use of three videotaped patients from psychiatry outpatients followed by observed live interviews with two patients, again from secondary care, all over the course of 1 day. Each case was discussed in detail to ensure that the interviewers were clear on the interpretation of each item. Following this structured training, the initial interviews carried out for the study were audiotaped, the patients having given their written informed consent, and rated jointly by the researchers and RM. RM provided feedback individually to the interviewers,

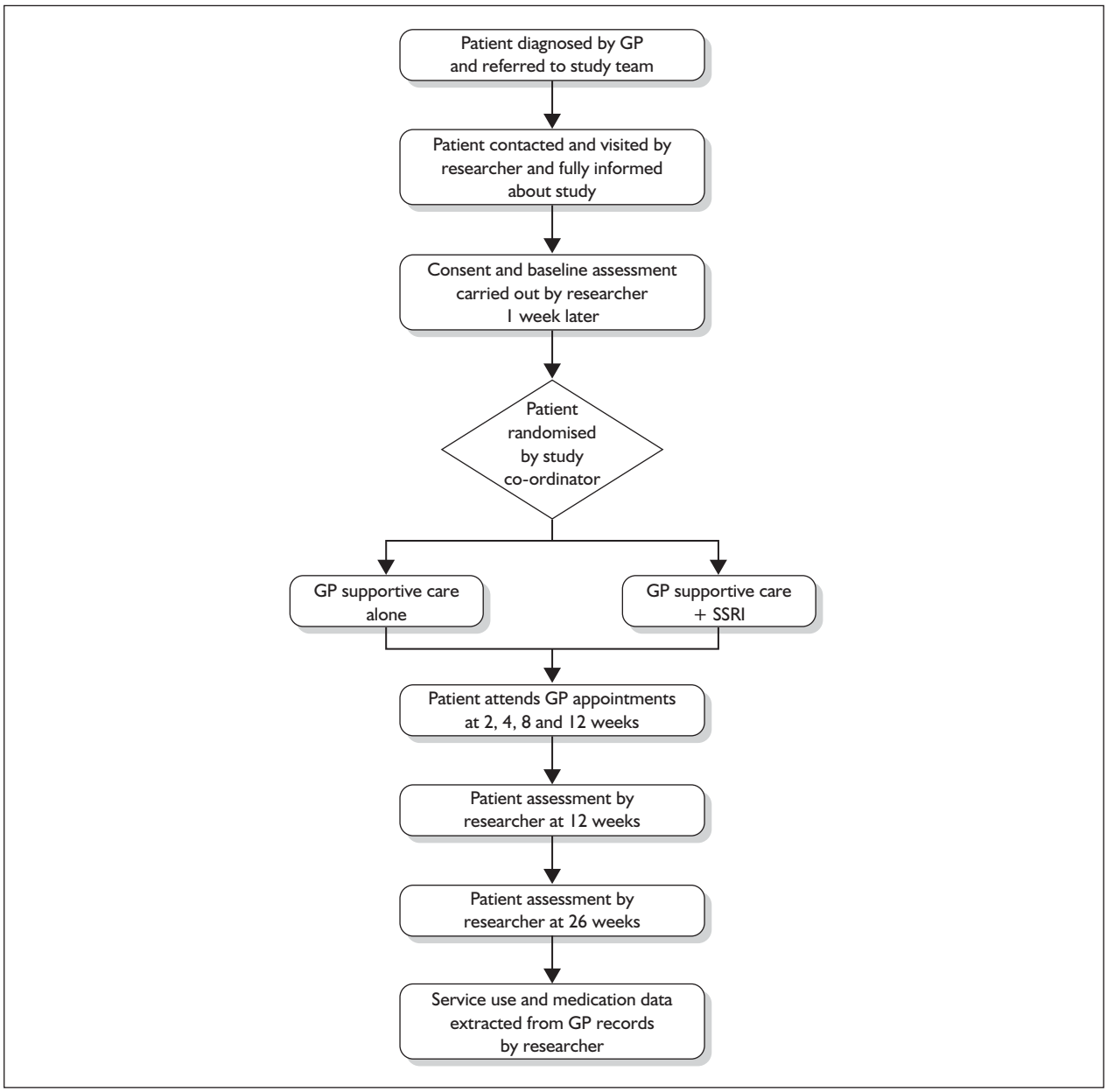

FIGURE 1 *Flow of patients through the study.*

then the three researchers and RM met to define issues of uncertainty, and to refine the interview and its scoring.

This was followed up 3 months later by RM who listened to audiotapes of the initial interviews carried out by the researchers, then met with them to provide further training to ensure uniformity of ratings. The inter-rater reliability of the HDRS ratings was assessed at four points during the 47 months of recruitment and follow-up: at 14, 17, 32 and 39 months. Each researcher was asked to audiotape all their HDRS interviews, as long as the patients gave consent, and to pass a random sample of them to a second researcher, who listened to the tape and independently rated all the items except those relating to non-verbal cues for 'agitation' and 'retardation'. Three tapes were selected at random at 14, 17 and 32 months, and five at 39 months. We used audiotaping because it is more acceptable and less intrusive to patients than videotaping. Patients selected for inclusion in the inter-rater reliability testing included some just below the range of severity for inclusion in the

study, some within the inclusion severity range, and some just above the severity for inclusion in the study. Patient interviews were included from both baseline and 12-week follow-ups. In this way, the inter-rater reliability across the whole range of scores from mild depressive symptoms to moderately severe depression was ascertained to check that patients were appropriately included into THREAD on the basis of severity and that they were reliably assessed at follow-up.

The Beck Depression Inventory (BDI) was used as a complementary measure of depressive symptoms (see Appendix 10).[61] This is a 21-item self-report inventory measuring characteristic attitudes and symptoms of depression, which has been validated for use in primary care.[62] As this is self-completed, it was considered that it should be free of observer bias and would enable a check to be carried out to ensure that there was no systematic bias in the HDRS ratings arising from possible unblinding of the researchers to treatment arm.

Quality of life

The Medical Outcomes Study Short Form 36-item (SF-36) questionnaire was used to measure health-related quality of life.[63] The responses to the 36 items can be condensed into scores in eight domains: physical functioning, role – physical, role – emotional, social functioning, bodily pain, vitality, mental health and general health (see Appendix 11). The SF-36 was also used to calculate quality-adjusted life-years (QALYs) to be used in the cost-effectiveness or cost–utility analysis.

Satisfaction with services received

Patient satisfaction was measured using the Medical Interview Satisfaction Scale (MISS),[64] a 29-item self-completed scale developed to assess the patient's satisfaction with the consultation. The scale was developed in the US but has been used previously in UK primary care practice.[65–68] Studies have compared it with other instruments,[66] have demonstrated that it has similar properties in the UK to those reported from the US and have linked scores with both patient-centredness[68] and enablement.[65] The scale consists of 29 items rated from 1 to 7 on a Likert range (very strongly disagree = 1 to very strongly agree = 7). The maximum score is therefore 7×29, i.e. 203. The 29 items include the patient's ratings of: the doctor's explanation of the illness and its seriousness; whether the doctor told the patient what they wanted to know; the doctor's interest in the person; the doctor's warmth; the doctor's friendliness; treatment of the patient as an equal; the doctor's understanding; relief of problems; relief of worries; and whether the patient felt they understood how to follow the doctor's advice (see Appendix 12).

Use of health services

To ascertain health-care costs in each arm, health services use was measured comprehensively using a modified version of the Client Service Receipt Inventory (CSRI)[69] at baseline and 26 weeks, asking about the previous 26 weeks at each point. Services measured included all contacts with GPs, other primary care professionals, psychiatrists, psychologists, community mental health nurses, counsellors, social care professionals and complementary therapists (see Appendices 13 and 14).

However, because patient recollection may not include all the services received over a 26-week period,[70] the patient's general practice medical record was also reviewed after the 26-week follow-up assessment. All GP consultations and other contacts with clinical practice staff were collected from the computerised records, along with outpatient and inpatient hospital contacts, referrals to counselling and psychological services, and any other treatment recorded at the practice. The dose and duration of any prescribed medications were also recorded. These data were collected for a period of 6 months before the date the patient entered the study as well as for the 6 months of participation in the study.

Costs of services used

The service use and medication data collected from the GP records were pooled with the CSRI data to maximise completeness (see Chapter 4 for which sources of data were used for which items of service use). Items of service use were multiplied by standard unit cost data to generate service costs for each patient.

Potential predictors

Sociodemographic questionnaire

A bespoke sociodemographic questionnaire was designed for the study, derived from previous trial instruments that have worked successfully. It included questions covering age, gender, ethnicity, marital status, accommodation, occupation and employment status (see Appendix 15), in order to

determine whether these factors were associated with a differential response to treatment.

Previous experience of depression and antidepressants

In the original proposal, we planned to use questions from the PSE-SCAN psychiatric interview[71] to determine the duration of depression and any past history of depression, in order to explore whether these factors were associated with a differential response to treatment. However, these questions would have significantly lengthened an already lengthy interview and so it was decided to replace them with a shorter bespoke questionnaire on the duration of the current episode of depression (asking when the patient last felt well, and how long they had felt *this* bad), previous episodes of depression (none, one, or more than one episode) and previous antidepressant treatment (yes or no, and how successful it was perceived to be). This change was approved by the MREC in July 2004. (The full questionnaire is reproduced in Appendix 16).

Life events and difficulties

The Life Events and Difficulties Schedule (LEDS) is usually used to collect information about stressful experiences over a 1-year period before onset/relapse of disorder. It differs from many other stress measures by distinguishing acute from ongoing stressors (events from difficulties), and by contrasting short- and long-term, and contextual and subjective ratings of these experiences. Specific qualitative aspects of stress such as losses, dangers, humiliations, entrapments, challenges and goal frustrations are also deliberately contrasted.[39] The shortened version of the LEDS (S-LEDS) was used in this study (see Appendix 17); essentially, this is rated using the same interview process, but the ratings concentrate on those events that are considered severe, with marked or moderate threat to the individual (and not on those that are deemed to carry only some or little threat), plus 'fresh start' experiences of the type found to predict depressive remission.

The three original researchers, a fourth researcher recruited later to replace one of the researchers who left, and the trial co-ordinator, all completed a week-long training course in London on the full LEDS with TH. She continued to support the researchers and regular consensus meetings were held to clarify any ambiguities that may have occurred with regard to the ratings of individual items.

Alcohol consumption

In a change to the original protocol, approved by the MREC, the AUDIT was added to measure alcohol consumption at baseline. This is a 10-item questionnaire, developed for the World Health Organization to screen for hazardous alcohol intake in primary health-care settings. It has high sensitivity and specificity and can be self-completed or administered in 2–4 minutes (see Appendix 18).[58]

Somatic symptoms

The BSI was used to measure somatic symptoms at baseline. This is a 46-item questionnaire about symptoms experienced in the last month, which was designed to detect physical symptoms that are commonly found in depressed patients (see Appendix 19).[51]

Symptom attribution

We considered it important to assess patients' attributions of their symptoms to physical or psychological causes, as a patient with a physical attribution might be more likely to respond to a physical treatment in the form of antidepressants. In the original proposal, we planned to use questions from the revised Illness Perception Questionnaire to assess symptom attribution at baseline. However, these questions would have significantly lengthened an already lengthy interview and so we decided instead to use a single question to determine the patient's broad attribution of their symptoms to one of three categories: physical cause; stress or emotional cause; or unknown cause (see Appendix 20). This change was approved by the MREC in July 2004.

Patient preference

Participating patients were asked to indicate, prior to randomisation, whether, if they had had a choice of treatments, they had a preference for supportive care without antidepressants, supportive care with antidepressants or no preference, in order to determine whether getting their choice of treatment was associated with a better outcome. The questions used are reproduced as Appendix 21.

Care received questionnaire

At both the 12- and 26-week follow-ups, the care received by participating patients in consultations was measured using a self-reported questionnaire designed specifically for the study (this was an addition to the original protocol). This included a range of depression-specific components of GP consultations, the Psycho-Socially Active Consultation (PSAC) questionnaire, in order to determine whether the support provided by the GPs was comparable in both arms in terms of potentially psychologically helpful consultation techniques. The components included discussion or advice on: tackling practical problems; taking more exercise; relaxation exercises; finding more leisure time; identifying enjoyable activities; addressing personal relationships; changing work patterns; and changing thought patterns. The questionnaire also included a question about patients' use of antidepressants and four questions devised by Morisky *et al.*[72] to measure patient adherence to the medication for those prescribed antidepressants, in either arm of the trial. (Appendix 22 shows the full questionnaire). In order to avoid unblinding the researchers, this questionnaire was completed while the researcher was out of the room and was placed in an envelope for direct transportation to the study co-ordinator, so that the researchers did not see any information on patients' use of antidepressants.

Data entry

The data arising from each baseline or follow-up interview were entered by each of the researchers as the study proceeded. A proportion of the data was double entered by the study co-ordinator JC (12 baseline interviews, ten 12-week interviews and ten 26-week interviews). Comparison of the two sets of data for these interviews confirmed the accuracy of the researchers' data entry. *Table 1* summarises the measures that were used at each point.

Sample size calculation

The sample size calculation was based on a planned analysis of the HDRS score as the primary outcome for two severity subgroups, corresponding to mild and moderate depression (with HDRS scores of 12–15 and 16–19 respectively). Hollyman *et al.*[73] found the standard deviation (SD) of the HDRS to be around 3.5, and reported roughly similar numbers of patients in these two severity ranges. We assumed this SD, equal numbers in the two subgroups and a pre–post correlation of 0.5.

Using analysis of covariance controlling for baseline values, we calculated that 49 patients at follow-up in each treatment/severity combination would allow the following effects to be detected at

TABLE 1 *Summary of baseline and follow-up measures*

Measures	Baseline	12-week follow-up	26-week follow-up
Outcomes			
17-item Hamilton Depression Rating Scale (HDRS) interview	✓	✓	✓
Beck Depression Inventory (BDI)	✓	✓	✓
Medical Outcomes Study Short Form 36-item (SF-36) questionnaire	✓	✓	✓
Medical Interview Satisfaction Scale (MISS)		✓	✓
Client Service Receipt Inventory (CSRI)	✓		✓
Predictors			
Sociodemographic questionnaire	✓		
Previous experience of depression questionnaire	✓		
Short Life Events and Difficulties Schedule (S-LEDS)	✓		✓
Alcohol Use Disorders Identification Test (AUDIT)	✓		
Bradford Somatic Inventory (BSI)	✓		
Symptom attribution questionnaire	✓		
Patient treatment preference questionnaire	✓		
Psycho-Socially Active Consultation (PSAC) questionnaire		✓	✓

a significance level of 0.05 (standard effect sizes in brackets): an overall average difference in HDRS scores between the two treatment arms of 1.4 (0.4) with 90% power; an interaction (difference between effects in the two severity subgroups) of 2.5 (0.7) with 80% power; and a difference between treatment arms within the more severe group of 2.0 (0.6) with 90% power. The last two calculations were conservative (tending to underestimate the power) because we considered that the SDs could turn out to be lower within the severity subgroups. A difference of 1.4 on the HDRS is relatively small (SD 0.4) and any difference smaller than this we regarded as clinically insignificant. In the trial of amitriptyline by Hollyman *et al*.[73] the HDRS scores fell by a mean of around 10 points in the mildly depressed group and around 13 in the more severely affected group. Therefore, we calculated that the sample size should be sufficient to detect clinically significant differences.

We therefore needed to follow up 196 patients to detect these differences (98 in each of the two arms). To allow for up to 25% loss to follow-up at 12 weeks, we calculated that 261 (87 at each of the three sites) would be needed. The agreed initial aim was to recruit even more than that number, 300 patients in all, aiming for 100 at each recruitment site (Southampton, Liverpool and London).

Statistical analysis

The primary analysis was by intention to treat (all available data analysed in the groups as randomised) using double-sided significance tests. We used analysis of covariance, controlling for baseline value and recruitment site, to estimate the overall treatment effectiveness (difference between arms in HDRS score) at both follow-ups separately (with 12-week outcome as the primary outcome). Longitudinal analysis, in which 12-week and 26-week outcomes were modelled simultaneously, was also performed. Time point, and time point × treatment interaction effects were tested in these models. Baseline predictors of a lack of follow-up data ('missingness') at either follow-up were investigated by means of logistic regression, and the models of predictors of 12- and 26-week outcomes were refitted including these variables. In all models, the patient's GP was included as a random effect and, as a sensitivity analysis, the overall (longitudinal model) was also fitted including GP practice as an alternative random effect. The interaction between severity subgroup and treatment was also tested, and further exploratory analyses assessed the impact of other potential predictors.

The main aim of the economic analysis was to compare the two treatment groups in terms of mean costs and cost-effectiveness. A secondary aim was to examine differences between the subgroups defined by severity, if differences in effectiveness were found for the severity subgroups. Given that cost data are frequently skewed, which can cause a violation of the assumptions of standard significance tests, bootstrapped estimates (multiple resampling within treatment arms) were planned, so that mean costs could still be compared while imposing no prior assumptions regarding the data distribution.

Cost-effectiveness was expressed in terms of incremental cost-effectiveness ratios (ICERs) and cost–utility ratios. In addition, cost-effectiveness acceptability curves (CEACs) were generated, synthesising data on costs and outcomes, for varying levels of acceptability of costs.

Chapter 3

Recruitment, follow-up rates and inter-rater reliability

Recruitment of practices and GPs

Prior to commencement of the study, NHS R&D approval was sought from those PCTs closest to the study centres and most accessible for the research teams. Very early on in the process of recruitment, it became apparent that progress was going to prove challenging, and therefore it was essential to recruit new practices further afield. A rolling plan of seeking NHS R&D approval from additional PCTs was therefore introduced across all three centres, and throughout 2004, 2005 and 2006 the team wrote to successive groups of GPs, in practices progressively further away from the centres, asking for their interest in participating.

Table 2 shows that, around the three centres, 6015 GPs in1787 practices were approached, and 576 GPs (9.6% of those approached) were inducted into the study from 212 (11.8%) of the practices approached. It should be noted that the number of GPs agreeing to participate is an approximation. If a practice agreed to participate, and all the GPs were present when the research team visited to discuss the study, it was assumed that they were all interested in taking part but it was not possible to be certain that all doctors within any one practice had, in fact, agreed.

The Royal College of General Practitioners (RCGP)[74] estimated that there were 8451 practices in England in 2006, which means that during the course of the study approximately one in five of all practices in England were approached from the three centres.

Tables 3–5 show the number of GPs, by PCT, who were approached to assess their interest. *Table 3* shows that agreement to take part was secured from 10% of the GPs approached from 18.5% of the practices in PCTs around the Southampton centre. *Table 4* shows that the corresponding figures for the London centre were 10.9% of GPs from 8.9% of practices approached. *Table 5* shows that the figures for the Liverpool centre were 8.6% of GPs from 9.5% of practices approached.

Table 6 shows that, compared with the RCGP figures for England as a whole, the participating GPs were broadly representative in terms of gender and whether they were part time or full time. However, the study practices were larger on average than practices in England generally.

Table 7 shows the range of locations of participating practices by recruitment centre. In 30 cases (14%) no information was received from the practice manager or GPs about practice location.

Table 8 shows the number of practices and GPs who referred patients into the study by centre and the number of practices and GPs who had patients randomised into the study. Overall, only around half of the practices agreeing to participate actually referred patients into the study. Of those practices who did refer patients, only 37% overall had patients randomised into the study. The lowest ratio of randomised patients to referred patients was found in Liverpool. Reasons for this are considered in Recruitment of patients, below.

TABLE 2 *Overall numbers of practices and GPs approached and agreeing to participate*

Centre	Number of practices approached	Number of GPs approached	Number of participating practices	Number of participating GPs
Southampton	496	2181	92	218
London	471	1244	42	136
Liverpool	820	2590	78	222
Total	1787	6015	212 (11.8%)	576 (9.6%)

TABLE 3 *Number of practices and GPs approached and agreeing to participate in the study in each of the PCTs that gave NHS R&D approval around the Southampton centre*

Primary care trust	Number of practices approached	Number of GPs approached	Number of participating practices	Number of participating GPs
Blackwater Valley	21	94	6	10
Bournemouth	26	106	5	16
East Hampshire	30	125	5	22
Eastleigh & Test Valley	20	103	6	9
Fareham & Gosport	20	99	5	7
Guildford & Waverley	29	155	3	12
Isle of Wight	12	65	4	9
Kennet & North Wiltshire	22	93	0	0
Mid Hampshire	22	110	4	16
New Forest	24	114	4	5
Newbury & Community	11	61	1	4
North Dorset	15	56	4	8
North Hampshire	28	113	10	21
Poole	24	107	2	3
Portsmouth	29	107	6	16
Reading	29	117	1	1
South & East Dorset	23	107	3	7
South Wiltshire	22	81	8	19
Southampton City	38	173	11	22
Swindon	29	104	3	8
West Sussex	22	90	2	3
Total	496	2180	93 (18.7%)	218 (10%)

TABLE 4 *Number of practices and GPs approached and agreeing to participate in the study in each of the PCTs that gave NHS R&D approval around the London centre*

Primary care trust	Number of practices approached	Number of GPs approached	Number of participating practices	Number of participating GPs
Bromley	57	27	0	0
Croydon	65	88	9	30
Kingston	35	99	1	1
Lambeth	52	206	7	23
Lewisham	50	185	8	28
Richmond	34	97	1	2
Southwark	51	150	8	28
Sutton	65	221	3	11
Wandsworth	62	171	5	13
Total	471	1244	42 (8.9%)	136 (10.9%)

TABLE 5 *Number of practices and GPs approached and agreeing to participate in the study in each of the PCTs that gave NHS R&D approval around the Liverpool centre*

Primary care trust	Number of practices approached	Number of GPs approached	Number of participating practices	Number of participating GPs
Ashton, Wigan & Leigh	54	164	1	5
Bebington & West Wirral	17	63	2	2
Birkenhead & Wallasey	37	120	7	23
Bolton	58	176	5	13
Bury	33	104	1	4
Central Cheshire	31	167	5	34
Central Liverpool	61	150	12	38
Cheshire West	26	103	5	10
Chorley & South Ribble	37	109	0	0
Eastern Cheshire	23	114	3	13
Ellesmere Port & Neston	13	53	1	4
Halton	16	63	1	1
Heywood & Middleton	14	41	0	0
Knowsley	31	90	4	3
North Liverpool	22	63	4	18
Oldham	43	113	2	4
Preston	29	81	2	2
Rochdale	21	74	1	1
Salford	49	124	6	12
South Liverpool	17	51	4	12
Southport & Formby	20	72	0	0
South Sefton	33	85	4	8
St Helens	35	109	3	5
Trafford North	18	53	1	1
Trafford South	26	70	1	1
Warrington	31	123	1	1
West Lancashire	25	55	2	7
Total	820	2590	78 (9.5%)	222 (8.6%)

TABLE 6 *Comparison of THREAD GP profile with RCGP data for England*

	Female (%)	Part time (%)	Average list size of practice
THREAD GPs	38	29	7516
RCGP figures	40	25	6250

TABLE 7 *Location of practices agreeing to participate in the study*

Location	Southampton	London	Liverpool	Total
Rural [*n* (%)]	15 (16)	0	5 (6)	20 (9)
Semi-rural [*n* (%)]	16 (17)	0	9 (12)	25 (12)
Suburban [*n* (%)]	39 (43)	11 (26)	23 (29)	73 (34)
City [*n* (%)]	20 (22)	19 (45)	25 (32)	64 (30)
Missing [*n* (%)]	2 (2)	12 (29)	16 (21)	30 (14)
Total	92	42	78	212

TABLE 8 *Number of practices and GPs who referred patients and had patients randomised into the study*

	Southampton	London	Liverpool	Total
Number of practices agreeing to participate	92	42	78	212
Number of practices (%) who referred patients	57 (61.9)	21 (50.0)	37 (47.4)	115 (54.2)
Number of practices (%) who had patients randomised into the study	46 (50.0)	17 (40.4)	20 (25.6)	83 (39.1)
Number of GPs agreeing to participate	218	136	222	576
Number of GPs (%) who referred patients	93 (42.6)	26 (19.1)	58 (26.1)	177 (30.7)
Number of GPs (%) who had patients randomised into the study	62 (28.4)	19 (13.9)	27 (12.1)	98 (17)

The mean and range of referrals per practice was 5.23 (1–32) and the mean and range of patients randomised was 2.68 (1–15).

Recruitment of patients

During the recruitment phase of the study, between December 2003 and May 2007 (42 months), 602 patients in total were referred to the study team across the three centres. However, only 220 of these were actually randomised into the study. *Table 9* shows the reasons why the remaining 382 patients were either excluded or declined to participate having had the study explained to them in more detail.

Table 9 shows that more patients declined to take part in Liverpool, which was due mainly to a greater proportion having a strong preference against taking antidepressants (18%, versus 10% in Southampton and 10% in London), as well as a greater proportion declining to participate but giving no reason for their decision (7%, versus 3% in Southampton and 1% in London). Discussion with the Liverpool team about the reasons for this identified as a possible factor the apparently much greater availability of counselling in Liverpool than in London and Southampton. It seemed likely that patients in Liverpool had more options for treatment besides drug treatment and more support from the GP, because the waiting list for counselling was only a matter of days, compared with months in London and Southampton.

Partial preference pilot

A partial preference design was piloted in two of the three centres (Southampton and Liverpool) between January and April 2005, to explore whether this would increase the rate of referral into the study. (It was not piloted in London as the researcher there was on leave for January 2005.) The results of the partial preference pilot are shown in *Table 10*. This shows that, despite patients having the freedom to choose which treatment they would receive, the total number of patients referred into the study did not increase significantly during the preference pilot. Nor was there any reduction in the number of patients declining to take part (there was a reduction in the number of patients excluded, but this could not have been related to patient preference and so must have arisen by chance). Furthermore, the researchers reported

TABLE 9 *Reasons why patients referred were not randomised into the study*

	Southampton	London	Liverpool	Total
Number of patients referred into study	292	108	202	602
Reasons for exclusion				
Hamilton (HDRS) score > 19	19	8	13	40
Hamilton (HDRS) score < 12	31	9	7	47
Antidepressants received in last 12 months	17	7	26	50
Alcohol consumption too high	2	1	5	8
Personally known to the researcher	1	0	0	1
Currently receiving counselling	1	0	4	5
Drug misuse	0	1	0	1
Under 18	0	1	0	1
Suicide risk	2	2	5	9
Breastfeeding	0	0	1	1
Entered partial preference pilot	6	0	3	9
Total number (%) excluded	79 (27)	29 (27)	64 (32)	172 (29)
Reasons for declining to participate				
Strong preference against antidepressants	29	11	37	77
Strong preference for antidepressants	4	0	2	6
Unable to contact or failed to attend	20	6	16	42
Problem with the study arrangements	22	7	11	40
No longer feeling depressed or did not consider self depressed	11	3	6	20
Too unwell or distressed	0	0	1	1
No reason given	8	1	15	24
Total number (%) who declined	94 (32)	28 (26)	88 (44)	210 (35)
Total number (%) of patients randomised	119 (41)	51 (47)	50 (25)	220 (37)

TABLE 10 *Summary of piloting of partial preference design*

	September–December 2004	January–April 2005
Number of patients referred	85	87
Number of patients excluded	35	22
Number of patients who declined to take part	23	24
Number of patients who entered preference arms	–	9
Number of patients randomised	27	32

that three of the nine patients who entered the preference arms informed the researchers that they would have agreed to be randomised if choosing which arm they entered had not been an option. Therefore it was decided not to change over to a partial preference design, as it was apparent that, although more patients in total could have been enrolled into the study by including a preference arm, this seemed likely to be at the expense of reduced numbers in the two randomised arms. Maximising the numbers agreeing to be randomised was most important in order to fulfil the aims of the study.

Representativeness of patients randomised into the study

Table 11 shows the gender and age profiles of patients referred into the study, those randomised and those not randomised. This shows that those patients who were randomised were generally representative in terms of gender and age of the total number of patients referred into the study. Two-thirds of the patients were female, and 90% were of working age.

It was clear during the first 6 months of the study that the rate of referral of depressed patients into the study was very much lower than the rate of patients presenting with new episodes of depression to GPs in their surgeries. To explore reasons for this, those members of the Study Group who were practising GPs agreed to complete a tally of patients with depression seen in their surgeries, and to ask GP colleagues in their practices to do the same. Tallies were kept over four periods during patient recruitment, and each time the data collection evolved in the light of experience from the previous exercise, so that the later tallies included more information on why patients presenting with depression were not referred into the study. *Table 12* summarises the findings of the four periods.

Table 12 shows that new episodes of depression were uncommon, occurring in only 2.5% of consultations, and only around 1 in 10 eligible patients were referred into the study. *Table 13* shows the age and gender profiles of patients presenting

TABLE 11 *Gender and age profiles of patients referred into the study in comparison with those who were randomised*

	Male [*n* (%)]	Female [*n* (%)]	Age < 65 [*n* (%)]	Age ≥ 65 [*n* (%)]	Age missing [*n* (%)]	Total (*n*)
Patients referred into study	194 (32)	408 (68)	550 (91)	39 (6)	13 (2)	602
Patients randomised	67 (31)	153 (69)	208 (94)	12 (6)	0 (0)	220

TABLE 12 *Four surgery tallies collected between May 2004 and December 2006*

Tally period	Recording dates	Number of surgery sessions	Number of consultations	Number of patients already taking anti-depressants	Number of new cases	Number of patients referred (%)	Number of patients randomised (%)
1	20.5.04–24.11.04	167	2385	304	92	9 (10)	2 (2)
2	15.2.05–1.7.05	168	2126	244	41	6 (15)	1 (2)
3	4.10.05–10.2.06	182	2547	313	56	0	0
4	2.10.06–5.12.06	249	3613	Not recorded	76	7 (9)	3 (4)

TABLE 13 *Gender and age profiles of patients presenting in surgery with a new episode of depression in comparison with those referred into the study*

	Male [*n* (%)]	Female [*n* (%)]	Gender missing [*n* (%)]	Age < 65 [*n* (%)]	Age ≥ 65 [*n* (%)]	Age missing [*n* (%)]	Total (*n*)
Eligible patients presenting in surgery	32 (57)	18 (32)	6 (11)	46 (82)	4 (7)	6 (11)	56
Patients referred into study	194 (32)	408 (68)	0 (0)	550 (91)	39 (6)	13 (2)	602

with depression in the third tally period (October 2005 to February 2006) compared with those referred into the study over the whole recruitment period. There was no significant difference in terms of age between eligible patients presenting in surgery and patients referred into the study ($\chi^2 = 0.14$, df = 1, $p = 0.709$), but a lower proportion of male patients were referred into the study than presented in surgery ($\chi^2 = 20.58$, df = 1, $p < 0.001$).

More detail from the last of the four tallies is shown in *Table 14*, which gives the reasons why potentially eligible patients were not referred into the study. For this tally period, a total of 25 GPs returned forms (19 from Southampton and six from Liverpool), including information recorded during 249 surgeries involving 3613 consultations over a 2-month period between 2 October and 5 December 2006.

TABLE 14 *Reasons why potentially eligible patients were not referred into the study, from the fourth GP surgery tally exercise*

Reason	Number of patients
Total number presenting with a new episode of depression	76
Number of patients referred into study	7
Reason for not referring patient	
GP or patient has a preference for antidepressants	16
GP or patient has a preference against antidepressants	11
GP perceived level of severity to be too high	11
GP perceived level of severity to be too low	4
Patient received antidepressants in last year	5
Patient has been told about study and is thinking about it	4
Not asked about study	3
Declined to take part in study	3
Already having counselling or psychological treatment	2
Does not accept diagnosis of depression	1
Drug or alcohol misuse problem	2
Under 18 years of age	1
Result of HADS questionnaire pending	1
Has multiple physical pathology	1
Does not speak English	1
Has terminal disease	1
Postnatal	1
Not using contraception	1

Follow-up assessments

The first follow-up assessments were scheduled for as close as possible to 12 weeks (84 days) after the baseline assessment and the second for as close as possible to 26 weeks (182 days). *Table 15* shows the range of timing of the follow-up assessments.

The follow-up rates for each of the time points remained consistent throughout the study. *Figure 2* shows that a total of 186 patients were interviewed at the 12-week follow-up and 167 at the 26-week follow-up. *Table 16* shows the follow-up rates for each of the three recruiting centres.

Patients were encouraged to make appointments for the next follow-up assessment by the researchers at the baseline or 12-week interview, but this was not always possible. If they did, letters were sent out 2 weeks prior to the appointment to remind them and the researcher would carry out the visit as planned. Sometimes the patient did not attend, in which case repeated attempts were made, if necessary, to contact the patient by means of telephone calls and letters to reschedule the follow-up visit. If no contact was made within 4 weeks, it was considered inappropriate to continue to pursue the patient at that time point, but patients unobtainable at 12 weeks were contacted again when the 26-week time point was reached. *Figure 2* shows that in five cases it was possible to collect data at the 26-week time point for patients who had not been followed-up at the 12-week time point.

Figure 2 also shows that there was a slight difference in rate of follow-up between the SSRI plus supportive care group and the supportive care alone group at the 12-week follow-up point (86% versus 83%), which became greater at the 26-week follow-up (80% versus 71%).

TABLE 15 *Timing of follow-up assessments*

	12 weeks (84 days)	26 weeks (182 days)
Number of patients	186	167
Mean days from baseline	91	191
Range	73–131	157–245

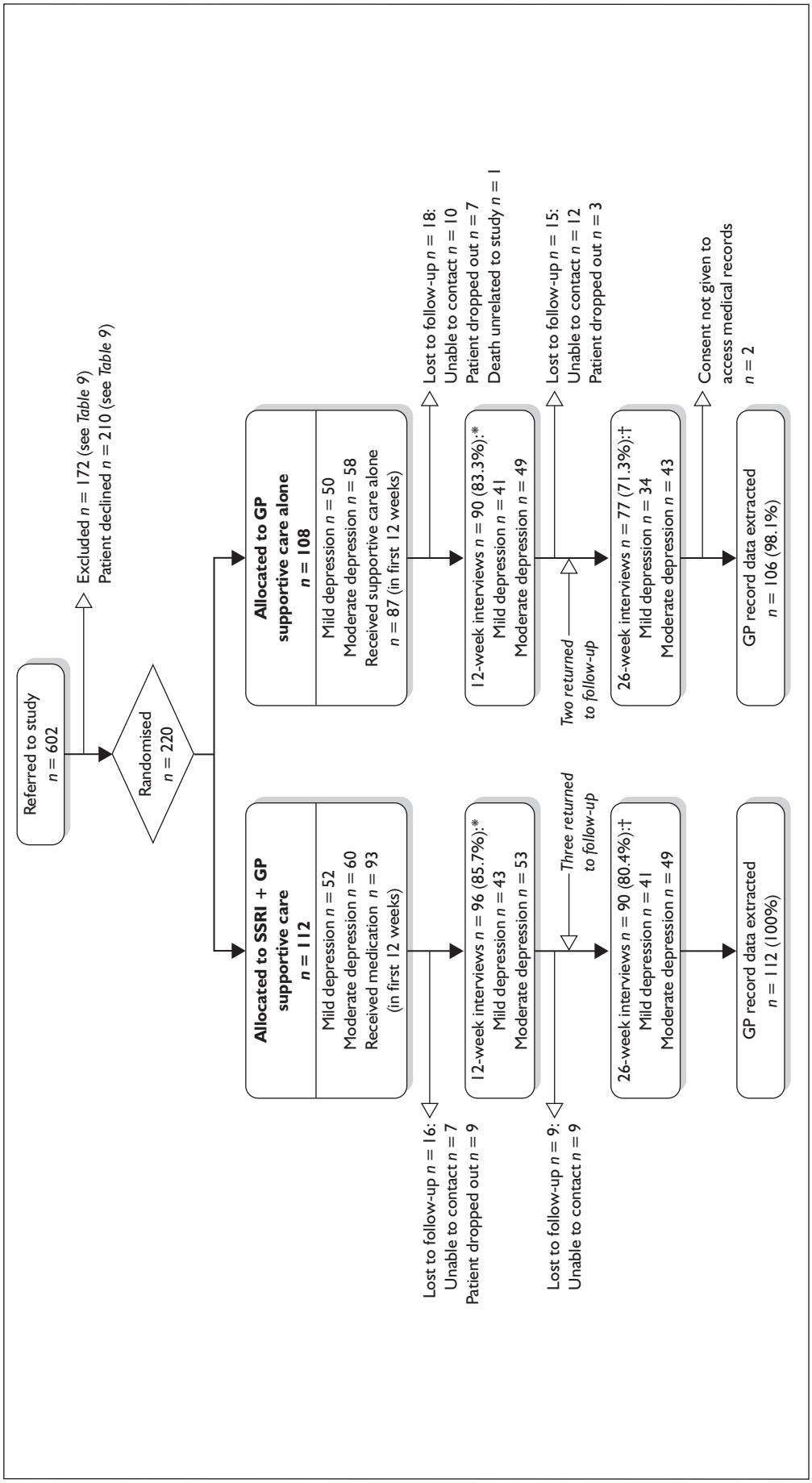

FIGURE 2 *CONSORT diagram. * 84.5% follow-up at 12 weeks; † 75.9% follow-up at 26 weeks.*

TABLE 16 *Follow-up rates for each of the three recruiting centres*

Centre	Number randomised	12-week follow-up completed [*n* (%)]	26-week follow-up completed [*n* (%)]
Southampton	119	105 (88.2)	98 (82.3)
London	51	39 (76.4)	29 (56.8)
Liverpool	50	42 (84)	40 (80)
Total	220	186 (84.5)	167 (75.9)

Blindness of researchers to allocation of patients

Remote telephone randomisation of the patients was carried out by the study co-ordinator after the baseline assessment, in order to keep the researchers blind to patient allocation. In addition, it was stressed to the patients at the start of the assessments that when the researchers went back to visit them, they must not tell the researchers to which arm they had been randomised. However, it proved impossible to maintain blindness in a number of cases, as shown in *Table 17*. Overall, at the 12-week interviews, failure of blinding occurred in 46 (25%) cases and at 26 weeks this rose to 53 (32%).

Inter-rater reliability

The inter-rater reliability of the HDRS ratings was assessed at 3 months, as described in Chapter 2, and again at four points during the 47 months of recruitment and follow-up: at 14, 17, 32 and 39 months (October 2004, January 2005, April 2006 and November 2006). Data from all possible pairs of the four raters were obtained in each of the four inter-rater reliability sessions. Within a session, each researcher took the role of primary rater (having taped the interview) an equal number of times, and everyone re-rated each other's tapes, so that raters and modes of rating were balanced within sessions. Each patient provided two sets of ratings, apart from one, who was assessed by two pairs of raters. A total of 84 ratings from 10 different pairs of raters for 42 patients were available. The patients included in the inter-rater reliability exercise had a mean age of 43.7 years (SD 17.1, range 18–78); 31 (87%) were female; and patients had a mean total score on the 17-item HDRS of 14.9 (SD 4.8, range 5–27). Sixty-six per cent of the total HDRS scores were in the 12–19 range used for inclusion in the THREAD study.

For individual items, the distribution of scores for the primary rater was examined, and overall percentage agreement and both weighted and unweighted kappa statistics were calculated. Weights were lower for disagreements that were further apart (*Table 18*).

TABLE 17 *Failure to maintain blindness of the researchers to patient allocation to arms, by follow-up point and by recruiting centre*

Number of interviews	Supportive care alone	SSRI plus supportive care	Total
12-week follow-up	***n = 90***	***n = 96***	***n = 186***
Southampton (*n* = 105)	12	11	23 (22%)
London (*n* = 39)	3	9	12 (31%)
Liverpool (*n* = 42)	4	7	11 (26%)
Total	17 (21%)	29 (28%)	46 (25%)
26-week follow-up	***n = 77***	***n = 90***	***n = 167***
Southampton (*n* = 98)	9	16	25 (26%)
London (*n* = 29)	3	10	13 (45%)
Liverpool (*n* = 40)	8	7	15 (37%)
Total	20 (26%)	33 (37%)	53 (32%)

TABLE 18 *Inter-rater agreement for individual items on HDRS*

Item		Responses of primary interviewer (%) (*n* = 42)				Unweighted		Weighted[a]	
		0	1	2	3	Agreement (%)	Kappa	Agreement (%)	Kappa
1	Depressed mood	11	25	51	13	67	0.49	88	0.59
2	Guilt	21	24	55	–	86	0.77	95	0.83
3	Suicidality	69	17	12	2	74	0.47	90	0.59
4	Initial sleep	45	19	36	–	88	0.81	94	0.88
5	Middle sleep	24	24	52	–	86	0.76	93	0.83
6	Delayed sleep	29	38	33	–	81	0.71	90	0.78
7	Work and interests	12	24	59	5	76	0.60	92	0.70
10	Psychic anxiety	5	26	67	2	88	0.75	96	0.78
11	Somatic anxiety	14	45	38	2	76	0.63	92	0.71
12	Gastrointestinal	59	36	5	–	83	0.69	92	0.73
13	Somatic, general	9	31	60	–	74	0.54	87	0.61
14	Genital symptoms	48	19	33	–	90	0.85	93	0.85
15	Hypochondriasis	93	7	–	–	95	0.48	95	0.48
16	Weight	76	7	17	–	95	0.88	96	0.90
17	Insight	76	24	–	–	74	0.30	74	0.30

a Weights were 1, 0.6667, 0.3333 and 0 for categories 0, 1, 2 and 3 respectively.

Most weighted kappa coefficients were above 0.6, indicating good agreement; the items for depressed mood and suicidal tendencies were just below this level. The kappa for hypochondriasis was relatively low, but this item had a very skewed distribution, with only 7% having a positive rating. Insight appeared to be the most difficult to rate, with a weighted kappa of only 0.3 and overall agreement of 76%.

Table 19 shows the inter-rater agreement for the total scores in each of the four sessions and overall. Total scores were pro-rated from 15 items to the equivalent of 17 items because items 8 and 9, retardation and agitation, were visually assessed and could not be rated from the audiotapes. Both intraclass correlations (and concordance coefficients, which are not shown as they were almost identical) showed very good agreement in all sessions. The overall estimate of the measurement variance was 1.55 (standard error 0.75), equivalent to a measurement error for an individual score of 1.25. The measurement error decreased in session 3 but the patient-level variance also decreased, thus resulting in a slightly lower reliability coefficient. However, this difference was not statistically significant. There was no evidence of systematic bias, with one rater tending to score higher or lower than the others (based on a regression with raters as fixed effects), or bias between the primary ratings and the corresponding secondary ratings, based on audiotapes (using paired *t*-tests).

TABLE 19 *Inter-rater agreement for total HDRS scores (pro-rated from 15 items)*

	Intraclass correlation	Standard error of measurement
Session 1	0.968	1.28
Session 2	0.937	1.49
Session 3	0.896	1.02
Session 4	0.938	1.24
Overall	0.947	1.25

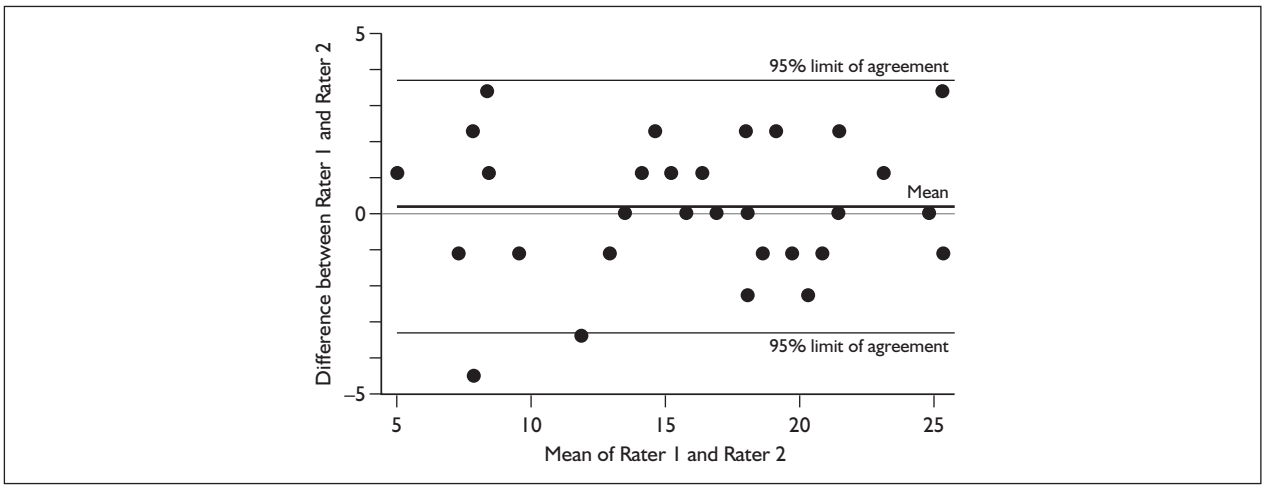

FIGURE 3 *Difference in HDRS scores between two raters on the same individuals plotted against their mean score.*

Figure 3 shows the difference between a pair of raters in total HDRS score plotted against the level of severity of depression as reflected in the average HDRS score; there is no evidence of variation in measurement error with severity.

The reference range (–3.31 to 3.69) shows where 95% of the points lie; only one point is outside these limits. The proportion who would have been assigned to a different severity subgroup depending on the rater was 2/42 (5%).

Chapter 4

Results: depression, generic health status and patient satisfaction

This chapter presents the results for effectiveness in terms of changes in the primary outcome, the HDRS score at 12 weeks. Results for the HDRS score at 26 weeks are also presented, followed by analyses of covariance of the HDRS scores at both follow-up points. This is followed by a longitudinal analysis taking both follow-ups into account simultaneously, and similar analyses of the other secondary outcome measures, the BDI score, the SF-36 score and the MISS score. As outlined in the analysis plan (see Chapter 2), the analyses were performed according to intention-to-treat principles (analysing all available data in the groups as randomised independent of the treatment that patients actually received), although some very preliminary results from 'compliers only' and 'blinded only' are also reported. Interactions between severity group and treatment arm were tested in the models, which included the baseline value of the outcome variable, to adjust for initial severity, recruitment centre and GP as a clustering effect. Treatment effects were also estimated (based on models including treatment × severity interaction terms) for typical members of each subgroup at baseline, e.g. a patient with baseline HDRS 13.5 compared with one whose baseline HDRS was 17.5.

The initial models included only those patients for whom we had complete follow-up. In addition, as there were missing data at follow-up, additional models including covariates significantly associated with having values for the outcomes missing at follow-up (missing status) were fitted. This approach is consistent with the guidance given on www.lshtm.ac.uk/msu/missingdata/guidelines.pdf. Its validity depends on the missing at random (MAR) assumption, i.e. missing status depends only on observed variables). The severity levels at the preceding time point (baseline for 12 weeks and 12 weeks for 26 weeks) were examined first, and then other potential missing value predictors were identified using logistic regression with missing status as the dependent variable, and recruitment centre and other potential missingness predictors as independent variables. A backward selection procedure was employed using $p = 0.1$ as the significance cut-off for rejecting variables, but always including the recruitment centre. Variables were re-entered into the final model one by one. The missingness predictors were analysed for both the 12-week and 26-week follow-up points and were found to be the same for both.

Although the 12-week HDRS score was the declared primary outcome, the statistically optimal analysis is that based on the longitudinal model, including both follow-up points and taking account of missing value predictors. This is because it makes use of all available data and therefore produces the most precise estimates, and because it takes account of any potential bias due to missing values, as far as possible given the available data. An analysis of potential predictors of outcome was also performed for the HDRS outcome over both follow-up points, including the prespecified potential predictors (listed in Chapters 1 and 2). A similar selection strategy to that described above was employed for the missingness predictors. Interactions between treatment arm and each potential predictor were also tested in these models, to determine whether they predicted response to SSRI treatment. Logistic models for remission to a value of below 8 on the HDRS and to below 50% of the initial HDRS level were also fitted.

STATA version 10 commands *xtreg* (mle) and *xtmixed* for continuous outcomes, and *xtlogit* and *xtmelogit* for binary outcomes were used.

Descriptive data

As described above, a total of 602 patients were referred into the study by 177 GPs from 115 practices. Of these, 172 (29%) were excluded and 210 (35%) declined to participate, so 220 patients were randomised: 112 to SSRI plus supportive care and 108 to supportive care alone. In the sample analysed at follow-up, there were 186 patients from 103 GPs (average 1.8 patients per GP, range 1–8) at 12 weeks and 167 patients from 96 GPs (average 1.7 patients per GP, range 1–7) at 26 weeks. For the primary outcome (HDRS), 162 patients had both

12- and 26-week data; 29 had neither follow-up, 24 had only the 12-week follow-up; and five had only the 26-week follow-up. Intraclass correlations by GP (after controlling for arm, centre and baseline value) were 0 and 0.012 at 12 and 26 weeks respectively.

Patient characteristics at baseline

Table 20 shows baseline characteristics of the randomised patients. The two arms were well balanced with the exception that the proportions of single people and those with a severe interpersonal difficulty were somewhat higher in the supportive care alone arm. Baseline HDRS, SF-36 and BSI scores were very similar. The BDI score was slightly higher in the supportive care alone arm.

Changes in the study outcome measures between baseline and follow-up

Table 21 shows the mean scores (and SDs) found for the primary and secondary outcome measures at baseline and follow-up. This demonstrates a fall at both follow-up points in HDRS and BDI score, and increases at both time points in the subscales of the SF-36, particularly the vitality (VT) and mental health (MH) subscales, in both arms of the trial. It also shows slightly greater patient satisfaction scores at both follow-up points in the SSRI plus supportive care arm, although the score in the SSRI plus supportive care arm at 26 weeks is slightly lower than at 12 weeks.

Missing values at follow-up

In comparison with the number of patients completing the HDRS at baseline, at the 12-week follow-up there were 18 missing values for the HDRS in the supportive care alone arm and 16 in the SSRI plus supportive care arm, due to incomplete follow-up of patients. At 26 weeks, there were 31 missing values for the HDRS in the supportive care alone arm and 22 in the SSRI plus supportive care arm. Those missing HDRS scores at 12 weeks were very little different at baseline than those for whom scores were available (means 15.12 versus 15.64 respectively, $p = 0.214$) and, similarly, those missing 26-week scores (but who had 12-week scores) were no more or less severe at the 12-week stage than those not lost to follow-up (means 9.62 versus 9.98, $p = 0.773$).

For the BDI, the numbers of missing values at 12 weeks were 19 and 16 for the two arms respectively, and at 26 weeks, 32 and 24 respectively. For the SF-36, the corresponding figures for the two arms were 3 and 2 at baseline, 22 and 21 at 12 weeks, and 36 and 27 at 26 weeks respectively. For the MISS, the corresponding figures for the two arms were 19 and 18 at 12 weeks, and 34 and 23 at 26 weeks respectively. The baseline values for patients missing at 12 and 26 weeks are shown in *Table 22*. Baseline patient characteristics, including age, gender, ethnicity, previous depression, previous antidepressant treatment, marital status, accommodation status, employment status, HDRS score, BDI score and BSI score, were examined to determine whether they predicted missing status at 12 and/or 26 weeks.

Younger age at randomisation, recruitment through the London centre and lack of employment were found to be significantly associated with patients being missing at follow-up, for both the 12- and 26-week follow-up points. Age at randomisation, centre, and employment status were therefore included in the analyses of covariance and longitudinal models described below.

Primary outcome

HDRS scores at 12 weeks

Table 23 and *Figure 4* show the baseline and 12-week HDRS scores by treatment arm and severity subgroup. It can be seen that the mean HDRS score fell on average in all four groups, but that in each of the two severity subgroups the fall was greater in the SSRI plus supportive care arm.

Figure 4 expresses graphically the results shown in *Table 23*, showing that the difference between trial arms persisted for both subgroups, although attenuated slightly, at the 26-week follow-up.

The box plots in *Figure 5* show the variability in the HDRS scores at both follow-up points. The relatively low variability at baseline resulted from the specified inclusion criterion of an HDRS score of 12–19. The plots show that, in terms of their HDRS scores, most patients were better at follow-up but the variability in scores increased and some patients had worse scores at follow-up.

Numbers of patients achieving remission or significant improvement on the HDRS

Table 24 shows the numbers of patients achieving remission (a reduction to an HDRS score of less than 8) and the numbers achieving clinically important improvement (a 50% reduction in HDRS

TABLE 20 *Baseline characteristics of randomised patients by trial arm*

	Supportive care alone (*n* = 108)	**SSRI plus supportive care (*n* = 112)**
Age at randomisation		
Mean (range)	41.3 (19–83)	38.6 (18–75)
	[n (%)]	***[n (%)]***
Median[a]	38.9	37.4
Age 18–30	32 (30)	37 (33)
Age 31–64	67 (62)	70 (63)
Age 65 and over	8 (7)	5 (4)
Male gender	36 (33)	31 (28)
White ethnicity	96 (89)	99 (88)
Previous antidepressant treatment[b]	56 (46)	49 (44)
Previous depression[c]		
None	40 (37)	41 (37)
Once	42 (39)	38 (34)
Twice or more	25 (23)	32 (29)
Severity subgroup		
Mild (HDRS 12–15)	51 (47)	52 (46)
Moderate (HDRS 16–20)	57 (53)	60 (54)
Centre		
Southampton	58 (54)	61 (54)
London	25 (23)	26 (23)
Liverpool	25 (23)	25 (22)
Marital status		
Married/cohabiting	56 (52)	63 (56)
Widowed/separated/divorced	32 (30)	11 (10)
Single	20 (19)	37 (33)
Accommodation		
Owner-occupied	50 (46)	47 (42)
Housing association	23 (21)	26 (23)
Private rental	22 (20)	20 (18)
Job related	2 (2)	1 (1)
Parents	8 (7)	8 (7)
Other	3 (3)	10 (9)

continued

score from the baseline value) at the 12- and 26-week follow-up points.

At 12 weeks, 22 patients in the supportive care alone arm (24.4% of those followed up) had HDRS scores below 8, compared with 40 (41.7%) in the SSRI plus supportive care arm. The absolute risk reduction (ARR) was therefore 17.2% and the number needed to treat (NNT) to achieve one remission at 12 weeks was 6 (95% CI 4 to 26). At 26 weeks, the corresponding numbers in remission were 28 (36.4%) and 49 (54.4%) respectively, so the ARR was 18.1% and the NNT to achieve one remission at 26 weeks was also 6 (95% CI 3 to 31).

TABLE 20 *Baseline characteristics of randomised patients by trial arm (continued)*

	Supportive care alone (*n* = 108)	**SSRI plus supportive care (*n* = 112)**
Occupation[d]		
Employed	64 (59)	76 (68)
Unemployed	44 (41)	36 (32)
Provoking agent in year before baseline (yes)	82 (76)	78 (70)
Ongoing severe interpersonal difficulty at baseline (yes)	44 (41)	33 (29)
	Mean (SD)	***Mean (SD)***
BSI score	18.98 (8.51)	19.69 (7.24)
BDI score[e]	24.31 (7.42)	22.57 (6.71)
HDRS score	15.68 (2.46)	15.45 (2.09)

a Missing value: supportive care alone 1.
b Missing values: supportive care alone 2, SSRI plus supportive care 1.
c Missing values: supportive care alone 1, SSRI plus supportive care 1.
d Missing value: supportive care alone 2, SSRI plus supportive care 3.
e Missing value: SSRI plus supportive care 1.

TABLE 21 *Values for primary and secondary outcome measures at baseline and follow-up*

	Baseline [mean (SD)]		**12-week follow-up [mean (SD)]**		**26-week follow-up [mean (SD)]**	
Outcome measures	**Supportive care alone**	**SSRI plus supportive care**	**Supportive care alone**	**SSRI plus supportive care**	**Supportive care alone**	**SSRI plus supportive care**
HDRS[a]	15.68 (2.46)	15.45 (2.09)	11.22 (5.78)	8.73 (5.20)	9.73 (5.57)	7.92 (5.67)
BDI[a]	24.48 (7.57)	22.40 (6.74)	15.15 (9.62)	12.99 (8.51)	13.27 (9.14)	11.05 (8.20)
SF-36 scales[b]						
Physical functioning (PF)	70.48 (25.63)	73.93 (25.95)	73.93 (26.79)	77.62 (24.95)	75.52 (28.79)	77.96 (25.25)
Role – physical (RP)	43.69 (39.17)	43.99 (38.14)	57.10 (41.69)	56.45 (43.13)	65.33 (40.46)	60.23 (41.63)
Bodily pain (BP)	52.15 (22.66)	58.24 (22.35)	60.18 (26.13)	67.23 (24.99)	63.29 (26.24)	70.07 (27.83)
General health (GH)	47.48 (19.43)	49.75 (20.05)	53.52 (22.66)	57.25 (22.93)	61.31 (20.17)	60.16 (24.11)
Vitality (VT)	27.90 (16.68)	27.81 (17.58)	41.63 (23.86)	47.34 (23.55)	45.22 (24.78)	51.27 (23.67)
Social functioning (SF)	43.75 (18.99)	45.54 (22.19)	60.25 (25.04)	64.63 (26.29)	67.93 (27.49)	70.79 (25.90)
Role – emotional (RE)	19.18 (29.80)	16.97 (25.92)	41.38 (43.42)	52.51 (41.77)	57.21 (42.92)	58.71 (41.67)
Mental health (MH)	38.65 (14.55)	38.84 (13.97)	54.43 (21.19)	61.91 (19.99)	59.79 (19.94)	63.13 (19.53)
MISS[b]	_	_	148.48 (25.29)	157.12 (26.14)	149.88 (25.19)	154.88 (27.95)

a Lower values at follow-up indicate improvement.
b Higher values at follow-up indicate improvement.

TABLE 22 *Baseline characteristics of patients with missing HDRS data at 12 and 26 weeks*

	Supportive care alone		SSRI plus supportive care	
Follow-up point	**12 weeks**	**26 weeks**	**12 weeks**	**26 weeks**
	[n (%)] [a]	***[n (%)]*** [a]	***[n (%)]*** [a]	***[n (%)]*** [a]
Age at randomisation				
Mean (range)	40.6 (19–81)	37.56 (19–81)	27.9 (19–43)	31.23 (19–47)
Median	40.7	33.8	25.3	30.7
18–30	4 (4)	12 (11)	11 (10)	11 (10)
31–64	13 (12)	18 (17)	5 (5)	11 (10)
65 and over	1 (1)	1 (1)	0 (0)	0 (0)
Male gender	6 (6)	8 (7)	4 (4)	7 (6)
White ethnicity	15 (14)	26 (23)	13 (12)	18 (16)
Previous antidepressant treatment	7 (6)	16 (14)	7 (6)	9 (8)
Previous depression				
None	8 (7)	10 (9)	4 (4)	9 (8)
Once	7 (6)	12 (11)	7 (6)	7 (6)
Twice or more	3 (3)	9 (8)	5 (4)	6 (5)
Severity subgroup				
Mild (HDRS 12–15)	9 (8)	16 (14)	9 (8)	11 (10)
Moderate (HDRS 16–19)	9 (8)	15 (14)	7 (6)	11 (10)
Centre				
Southampton	7 (6)	14 (13)	7 (6)	7 (6)
London	6 (6)	11 (10)	6 (5)	11(10)
Liverpool	5 (5)	6 (5)	3 (3)	4 (4)
Marital status				
Married/cohabiting	5 (5)	13 (12)	9 (8)	11 (10)
Widowed/separated/divorced	9 (8)	10 (9)	–	1 (1)
Single	4 (4)	8 (7)	7 (6)	10 (9)
Accommodation status				
Owner/occupied	4 (4)	8 (7)	2 (2)	6 (5)
Housing association	7 (6)	11 (10)	3 (3)	7 (6)
Private rental	2 (2)	6 (5)	5 (4)	4 (4)
Job related	1 (1)	1 (1)	0	–
Parents	2 (2)	3 (3)	4 (4)	4 (4)
Other	2 (2)	2 (2)	2 (2)	1 (1)
Occupation				
Employed	11 (10)	16 (14)	9 (8)	12 (11)
Unemployed	6 (6)	13 (12)	7 (6)	10 (9)
	Mean (SD)	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***
Baseline HDRS score	15.28 (2.82)	15.65 (2.55)	14.94 (2.11)	15.27 (2.08)
12-week HDRS score	_	12.00 (7.45)	_	5.67 (5.10)
Baseline BDI score	25.33 (7.16)	25.27 (8.30)	24.69 (5.15)	22.59 (8.00)
Baseline BSI score	15.78 (8.29)	19.50 (8.87)	22.78 (8.76)	21.27 (7.51)

a Percentage missing out of total initial population in each arm.

TABLE 23 *Baseline and 12-week HDRS scores by treatment arm and severity subgroup*

		Supportive care alone		SSRI plus supportive care	
	Severity subgroup	**Number of missing values**	**Mean (SD)**	**Number of missing values**	**Mean (SD)**
HDRS at baseline	Mild (12–15)	–	13.34 (1.12)	–	13.54 (1.11)
	Moderate (16–19)	–	17.71 (1.15)	–	17.10 (1.01)
	Overall	–	15.68 (2.46)	–	15.45 (2.09)
HDRS at 12-weeks	Mild (12–15)	9	9.15 (4.95)	9	7.30 (5.05)
	Moderate (16–19)	9	12.96 (5.90)	7	9.89 (5.07)
	Overall	18	11.22 (5.78)	16	8.73 (5.2)
HDRS change from baseline	Mild (12–15)	9	4.32 (4.79)	9	6.28 (5.08)
	Moderate (16–19)	9	4.73 (5.67)	7	7.25 (4.78)
	Overall	18	4.54 (5.26)	16	6.81 (4.91)

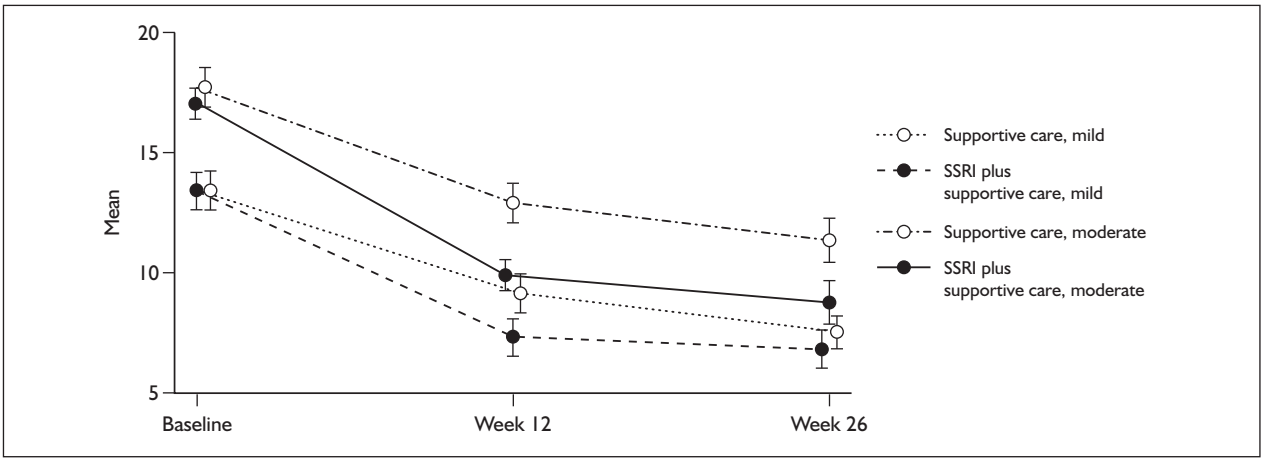

FIGURE 4 *Mean values for HDRS scores by treatment arm and severity subgroup (bars around mean values are standard errors).*

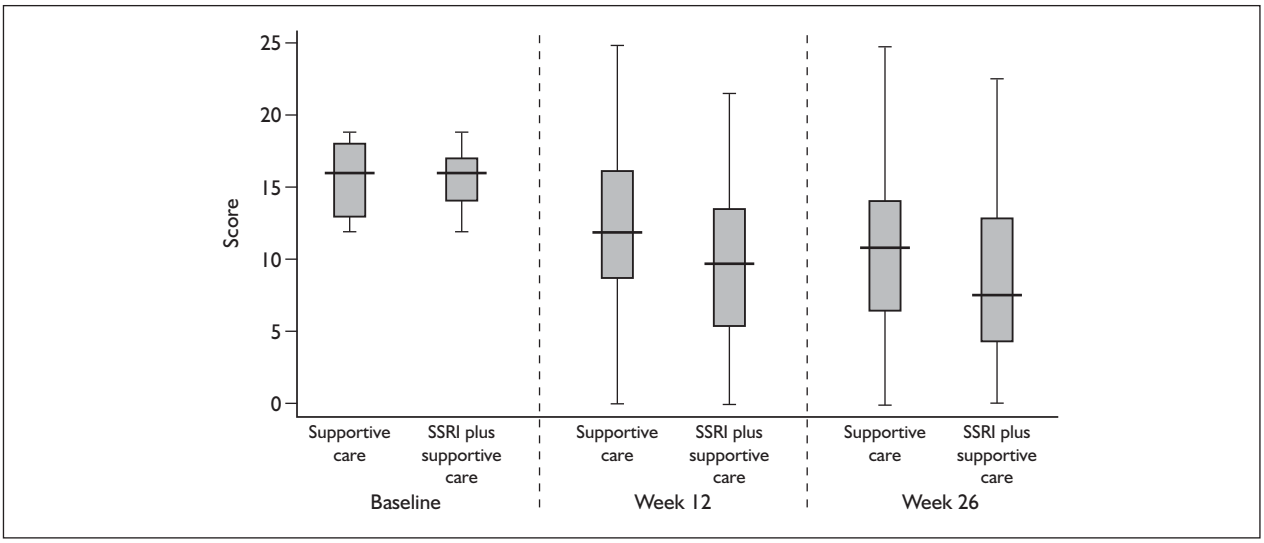

FIGURE 5 *Box plots of HDRS scores at each time point for the two trial arms.*

TABLE 24 *Number of patients achieving remission or significant improvement on the HDRS at 12 and 26 weeks, including breakdown by severity subgroup*

		12 weeks		26 weeks	
		Remission to < 8 [*n* (%)]	**Reduction by 50% [*n* (%)]**	**Remission to < 8 [*n* (%)]**	**Reduction by 50% [*n* (%)]**
Total sample	Supportive care alone	22 (24)	26 (29)	28 (36)	28 (36)
	SSRI plus supportive care	40 (42)	42 (44)	49 (54)	53 (59)
Mild subgroup (HDRS 12–15)	Supportive care alone	15 (37)	14 (34)	16 (47)	14 (41)
	SSRI plus supportive care	21 (49)	20 (47)	24 (59)	23 (56)
Moderate subgroup (HDRS 16–19)	Supportive care alone	7 (14)	12 (24)	12 (28)	14 (33)
	SSRI plus supportive care	19 (36)	22 (42)	25 (51)	30 (61)

At 12 weeks, 26 patients (28.9%) in the supportive care alone arm had a 50% or greater fall in HDRS score from baseline, compared with 42 (43.8%) in the SSRI plus supportive care arm. The ARR was therefore 14.9% and the NNT to achieve improvement in one patient at 12 weeks was 7 (95% CI 4 to 83). At 26 weeks, the corresponding rates of improvement were 28 (36.4%) and 53 (58.9%) respectively, so the ARR was 22.5% and the NNT to achieve improvement in one patient was 5 (95% CI 3 to 13).

Regression analyses for HDRS scores

Table 25 shows the results of the analysis of covariance for the primary outcome, the HDRS score at 12 weeks, including treatment arm, HDRS baseline score and recruitment centre, with the patient's GP fitted as a random effect. Treatment arm coefficients are for intervention versus control.

This shows a statistically significant difference between the treatment arms in HDRS depression scores after 12 weeks, after adjustment for baseline HDRS score, recruitment centre and clustering by GP. It also shows that baseline HDRS score was a statistically significant independent predictor of 12-week HDRS score. The differences between the arms for the two severity groups when analysed separately were –1.919 (95% CI –3.962 to 0.124) and –2.149 (95% CI –4.229 to –0.069) for the mild and moderate subgroups respectively. The interaction term (difference in treatment effect) for a 4-point increase in baseline severity was 1.10 (95% CI –3.73 to 1.54, $p = 0.414$) and the significance of the interaction with baseline severity as a continuous variable was $p = 0.773$, i.e. there was no evidence for a differential effect between the severity subgroups with respect to the differences between arms in HDRS scores.

Table 26 shows that the statistically significant differences in HDRS depression scores at 12 weeks between treatment arms remained after adjustment for the missingness predictors of age and employment status, along with baseline HDRS score, recruitment centre and GP. Once again, the interaction between arm and severity subgroup was not significant ($p = 0.667$).

TABLE 25 *HDRS scores at 12 weeks: analysis of covariance*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–2.293	–3.741 to –0.845	0.002
Baseline HDRS score	0.874	0.544 to 1.204	< 0.001
London vs Southampton	1.211	–0.658 to 3.080	0.204
Liverpool vs Southampton	1.287	–0.524 to 3.098	0.164

TABLE 26 *HDRS score at 12 weeks: analysis of covariance, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–2.091	–3.544 to –0.638	0.005
Baseline HDRS score	0.858	0.520 to 1.196	< 0.001
London vs Southampton	0.939	–0.935 to 2.814	0.326
Liverpool vs Southampton	1.018	–0.815 to 2.851	0.276
Age at randomisation	0.001	–0.051 to 0.054	0.962
Employment status (unemployed vs employed)	1.563	0.013 to 3.113	0.048

Table 27 shows the baseline and 26-week HDRS scores by treatment arm and severity subgroup. *Table 28* shows the results of the analysis of covariance for the HDRS score at 26 weeks, including treatment arm, HDRS baseline score and recruitment centre, with the patient's GP fitted as a random effect.

Table 28 shows that the difference between the treatment arms in changes in the HDRS depression scores after 26 weeks was of borderline statistical significance in this analysis, after adjustment for the other variables. The interaction term, for a 4-point increase in baseline severity, was –1.54 (95% CI –4.18 to 1.35, $p = 0.297$) and the significance of the interaction with baseline severity as a continuous variable was $p = 0.283$, indicating that there was no evidence for a differential effect between the severity subgroups with respect to the changes in HDRS scores.

TABLE 27 *Baseline and 26-week HDRS scores by treatment arm and severity subgroup*

		Supportive care alonew		SSRI plus supportive care	
	Severity subgroup	Number of missing values	Mean (SD)	Number of missing values	Mean (SD)
HDRS at baseline	Mild (12–15)	–	13.34 (1.12)	–	13.54 (1.11)
	Moderate (16–19)	–	17.71 (1.15)	–	17.12 (1.04)
	Overall	–	15.68 (2.46)	–	15.45 (2.09)
HDRS at 26 weeks	Mild (12–15)	16	7.56 (4.01)	11	6.83 (5.02)
	Moderate (16–19)	15	11.44 (6.06)	11	8.84 (6.05)
	Overall	31	9.73 (5.57)	22	7.92 (5.67)
HDRS change from baseline	Mild (12–15)	16	5.71 (4.29)	11	6.73 (5.22)
	Moderate (16–19)	15	6.19 (5.97)	11	8.27 (5.92)
	Overall	31	5.97 (5.27)	22	7.57 (5.64)

TABLE 28 *HDRS scores at 26 weeks: analysis of covariance*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.688	–3.326 to –0.049	0.043
Baseline HDRS score	0.606	0.238 to 0.974	0.001
London vs Southampton	1.157	–1.273 to 3.587	0.351
Liverpool vs Southampton	0.651	–1.465 to 2.766	0.547

The additional missingness predictors (age at randomisation and employment status) were included in the results shown in *Table 29*. Again, the difference between the treatment arms in changes in HDRS depression scores after 26 weeks was of borderline statistical significance after adjustment for the missingness predictors of age and employment status, along with the baseline HDRS score, recruitment centre and referring GP. The interaction between arm and severity subgroup was not significant ($p = 0.181$).

Longitudinal analysis of HDRS scores at 12 and 26 weeks

Maximum likelihood mixed-effects models were used for the longitudinal analyses, with GP and subject as random effects, and time as a covariate, coded as 1 for 12 weeks and 2 for 26 weeks. The 'time' coefficient, therefore, represents the drop in score over 14 weeks, averaged over both treatment arms. *Tables 30* and *31* show the results of the longitudinal analysis of HDRS scores at 12 and 26 weeks, excluding and including factors associated with missing status at either time point. Interaction between treatment arm and time was also included in the longitudinal models to test for any evidence for a drop-off or increase in effect over time. Although there was an overall reduction in HDRS scores over time, there was no evidence for a time × treatment interaction ($p = 0.574$). Severity by arm interaction was assessed using the baseline HDRS score as a continuous variable and, as with the separate time point analyses presented above, was found not to be significant ($p = 0.219$).

The model shown in *Table 31* includes the variables which were found to predict missingness. These analyses show that there is a highly significant effect of treatment arm over time when the outcomes at both 12 and 26 weeks are included. Once again, the severity by arm interaction was assessed and found not to be significant ($p = 0.378$). This time × treatment interaction was also tested using the baseline HDRS score as a continuous variable and was found not to be significant ($p = 0.239$).

Once again, HDRS scores at follow-up are significantly associated with baseline HDRS scores. In addition, employment status is a highly significant predictor of outcome, and the coefficient shows that the effect size is very similar to that of treatment status (with higher scores at follow-up among patients who were unemployed at baseline).

The results from *Table 31* are also illustrated in *Figure 6*, which gives predicted HDRS over time by treatment arm, adjusting for the other variables in the model. For illustration, the reference

TABLE 29 *HDRS score at 26 weeks: analysis of covariance, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.336	–2.951 to 0.278	0.105
Baseline HDRS score	0.620	0.251 to 0.990	0.001
London vs Southampton	0.839	–1.486 to 3.165	0.479
Liverpool vs Southampton	0.110	–1.958 to 2.179	0.917
Age at randomisation	0.024	–0.033 to 0.081	0.413
Employment status (unemployed vs employed)	2.594	0.865 to 4.322	0.003

TABLE 30 *Longitudinal analysis of HDRS scores at 12 and 26 weeks*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–2.145	–3.516 to –0.774	0.002
Baseline HDRS score	0.760	0.449 to 1.072	< 0.001
London vs Southampton	1.115	–0.668 to 2.899	0.220
Liverpool vs Southampton	0.878	–0.839 to 2.594	0.316
Time	–1.129	–1.794 to –0.464	0.001

TABLE 31 *Longitudinal analysis of HDRS scores at 12 and 26 weeks, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.866	–3.224 to –0.508	0.007
Baseline HDRS score	0.754	0.440 to 1.068	< 0.001
London vs Southampton	0.785	–0.980 to 2.549	0.383
Liverpool vs Southampton	0.471	–1.246 to 2.188	0.591
Time	–1.126	–1.795 to –0.457	0.001
Age at randomisation	0.014	–0.034 to 0.063	0.562
Employment status (unemployed vs employed)	–2.172	–3.621 to –0.722	0.003

baseline HDRS score has been set at 15.6, centre to Southampton, age to 40 and employment status to being currently employed.

Secondary outcomes

BDI scores

Table 32 shows the longitudinal analysis of BDI scores at 12 and 26 weeks. *Table 33* includes the variables that were found to predict missingness. These analyses show that the difference between the two treatment arms in depression scores on the BDI over time was not statistically significant, unlike that for the HDRS scores. Higher BDI scores at follow-up were predicted by higher baseline BDI scores, and were also strongly related to being unemployed at baseline. The test for interaction between arm and severity was not significant.

SF-36 scores

Statistically significant differences between the two treatment arms were found for the MH and VT subscales of the SF-36. No statistically significant differences were found for the remaining subscales. The actual values for all the subscales at baseline and follow-up are shown in *Table 21*, together with their SDs.

Mental health

Table 34 shows the longitudinal analysis of the MH subscale scores at 12 and 26 weeks. *Table 35* includes the variables that were found to predict missingness. These analyses show that differences between arms in MH scores were statistically significant after adjustment for the other variables in the model. Lower MH scores at follow-up were also predicted by lower baseline MH scores, and once again were strongly related to being unemployed at baseline.

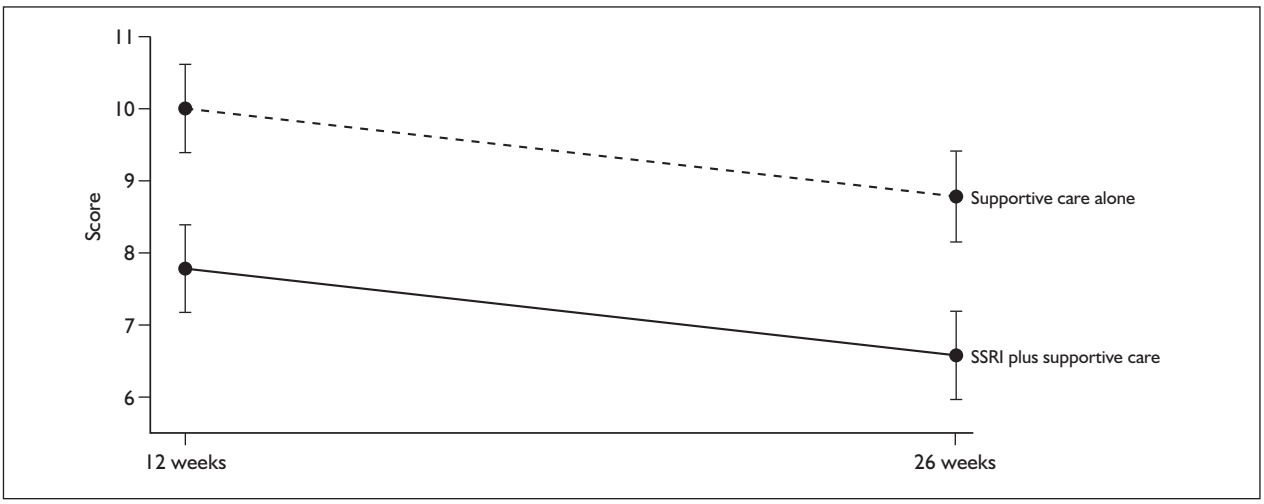

FIGURE 6 *Estimated mean difference in HDRS scores between treatment arms (longitudinal analysis of HDRS scores at 12 and 26 weeks, including missingness predictors). Bars around estimates give the standard errors. See* Table 31 *for model.*

TABLE 32 *Longitudinal analysis of BDI scores at 12 and 26 weeks*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.510	–3.692 to 0.671	0.175
Baseline BDI score	0.532	0.373 to 0.691	< 0.001
London vs Southampton	2.151	–0.637 to 4.939	0.130
Liverpool vs Southampton	0.768	–1.921 to 3.458	0.576
Time	–1.715	–2.680 to –0.749	< 0.001

TABLE 33 *Longitudinal analysis of BDI scores at 12 and 26 weeks, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.038	–3.184 to 1.109	0.343
Baseline BDI score	0.534	0.378 to 0.691	< 0.001
London vs Southampton	1.742	–1.008 to 4.492	0.214
Liverpool vs Southampton	0.040	–2.629 to 2.709	0.977
Time	–1.714	–2.684 to –0.745	0.001
Age at randomisation	0.069	–0.007 to 0.145	0.076
Employment status (unemployed vs employed)	–3.351	–5.633 to –1.069	0.004

TABLE 34 *Longitudinal analysis of SF-36 mental health (MH) subscale scores at 12 and 26 weeks*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	6.125	1.064 to 11.187	0.018
Baseline MH score	0.298	0.124 to 0.472	0.001
London vs Southampton	–6.822	–13.356 to –0.289	0.041
Liverpool vs Southampton	0.402	–5.879 to 6.685	0.900
Time	2.810	0.178 to 5.442	0.036

TABLE 35 *Longitudinal analysis of SF-36 mental health (MH) subscale scores at 12 and 26 weeks, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	5.049	0.038 to 10.060	0.048
Baseline MH score	0.294	0.121 to 0.468	0.001
London vs Southampton	–5.992	–12.500 to 0.516	0.071
Liverpool vs Southampton	2.163	–4.109 to 8.435	0.499
Time	2.873	0.228 to 5.517	0.033
Age at randomisation	–0.111	–0.290 to 0.691	0.228
Employment status unemployed vs employed)	6.335	0.958 to 11.711	0.021

Vitality

Table 36 shows the longitudinal analysis of the VT subscale scores at 12 and 26 weeks. The analysis in *Table 37* also includes the variables that were found to predict missingness. These analyses show that differences between arms in the VT scores were statistically significant after adjustment for baseline VT score, centre and GP (*Table 36*). The relationship was found to be slightly weaker after adjustment for the variables that predicted missingness (*Table 37*), and no longer quite statistically significant at the 5% level. In addition, *Table 37* shows that lower VT scores at follow-up were predicted by lower baseline VT scores and by being older at baseline.

Patient satisfaction

Table 38 shows the longitudinal analysis of the MISS scores at 12 and 26 weeks, including baseline HDRS score (as baseline MISS scores were not available) and the variables that were found to predict missingness. This shows that satisfaction scores were significantly different between the treatment arms, with higher scores among patients in the SSRI plus supportive care arm. However, although the differences were statistically significant, they were not large differences in absolute magnitude (as shown in *Table 21*). None of the other factors in the model below were found to predict satisfaction.

TABLE 36 *Longitudinal analysis of SF-36 vitality (VT) subscale scores at 12 and 26 weeks*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	6.465	0.622 to 12.307	0.030
Baseline VT score	0.457	0.281 to 0.633	< 0.001
London vs Southampton	–5.631	–13.275 to 2.013	0.149
Liverpool vs Southampton	–1.450	–8.700 to 5.800	0.695
Time	3.309	0.270 to 6.347	0.033

TABLE 37 *Longitudinal analysis of SF-36 vitality (VT) subscale scores at 12 and 26 weeks, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	5.186	0.558 to 10.930	0.077
Baseline VT score	0.435	0.263 to 0.608	< 0.001
London vs Southampton	–5.045	–12.616 to 2.526	0.192
Liverpool vs Southampton	0.608	–6.582 to 5.780	0.868
Time	3.337	0.280 to 6.394	0.032
Age at randomisation	–0.259	–0.462 to –0.056	0.012
Employment status (unemployed vs employed)	6.383	0.195 to 12.570	0.043

TABLE 38 *Longitudinal analysis of patient satisfaction (MISS) scores at 12 and 26 weeks, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	7.791	1.145 to 14.438	0.022
Baseline HDRS score	–0.187	–1.685 to 1.311	0.806
London vs Southampton	–4.585	–14.594 to 5.424	0.369
Liverpool vs Southampton	3.395	–6.030 to 12.821	0.480
Time	–1.522	–4.400 to 1.356	0.300
Age at randomisation	0.169	–0.073 to 0.411	0.172
Employment status (unemployed vs employed)	–0.329	–7.353 to 6.696	0.927

The MISS data will undergo factor analysis for comparison with the previous literature on the use of the scale, and further analyses will be presented in a subsequent publication.

Exploratory analysis of predictor variables

Predictors of outcome

An analysis of potential predictors of outcome was also performed for the HDRS score over both follow-up points, including the prespecified potential predictors (listed in Chapters 1 and 2). A similar selection strategy was employed, as described above, for the missingness predictors (backward selection using a criterion of $p = 0.1$, retaining centre, baseline score and GP). Interactions between treatment arm and each potential predictor were also tested in these models.

Tables 39 and *40* show the results of regression analyses, including the predictors listed in the analysis plan outlined in Chapter 2. The two analyses differed only in terms of which LEDS variable was included. *Table 39* includes any provoking agent in the year before randomisation, whereas *Table 40* includes any ongoing severe interpersonal difficulty at baseline.

Interaction between age and gender was found to be not significant. As the number of predictors was large, those which were not significant at the level of $p = 0.1$ were removed in a backward selection procedure (keeping missingness predictors and centre, baseline level and GP as a clustering effect in the model). The results of the backward selection are presented in *Table 41*.

Table 41 confirms that a better outcome, in terms of HDRS averaged scores over the 12- and 26-week follow-up points, is significantly related to being randomised to the SSRI plus supportive care arm, even after adjusting for the other potential predictors measured. In addition, a greater initial severity of depression, being unemployed and having more physical symptoms at baseline were significant predictors of a poorer outcome for depression. The interaction between treatment and time was not significant ($p = 0.574$).

TABLE 39 *Longitudinal analysis of potential predictors of HDRS scores at follow-up, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.719	–3.219 to –0.220	0.025
Baseline HDRS score	0.563	0.198 to 0.928	0.002
London vs Southampton	0.971	–1.438 to 3.380	0.429
Liverpool vs Southampton	0.427	–1.727 to 2.581	0.698
Time	–0.993	–1.751 to –0.236	0.010
Age at randomisation	0.010	–0.058 to 0.079	0.771
Employment status (unemployed vs employed)	1.475	–0.284 to 3.233	0.100
Gender	–1.270	–3.067 to 0.528	0.166
Ethnicity – black vs white	0.251	–3.729 to 4.232	0.901
Ethnicity – other vs white	0.525	–4.339 to 5.390	0.832
Widowed/separated/divorced vs married/cohabiting	0.067	–2.002 to 2.137	0.949
Single vs married/cohabiting	1.426	–0.459 to 3.310	0.138
Duration of symptoms	0.003	–0.005 to 0.011	0.507
Baseline BSI score	0.185	0.081 to 0.290	0.001
Perceived cause: physical vs other	0.029	–1.974 to 2.033	0.977
Previous anti-depressant treatment (yes vs no)	0.614	–1.034 to 2.261	0.465
Alcohol use (AUDIT score)	–0.004	–0.242 to 0.234	0.972
LEDS provoking agent in year before	0.102	–1.659 to 1.863	0.909

AUDIT, Alcohol Use Disorders Identification Test; BSI, Bradford Somatic Inventory; LEDS, Life Events and Difficulties Scale.

TABLE 40 *Longitudinal analysis of potential predictors of HDRS scores at 12 and 26 weeks follow-up, including missingness predictors*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.584	–3.071 to –0.067	0.037
Baseline HDRS score	0.571	0.210 to 0.931	0.002
London vs Southampton	0.728	–1.712 to 3.168	0.559
Liverpool vs Southampton	0.250	–1.923 to 2.423	0.822
Time	–1.000	–1.757 to –0.245	0.010
Age at randomisation	0.014	–0.054 to 0.081	0.693
Employment status (unemployed vs employed)	1.429	–0.310 to 3.169	0.107
Gender	–1.152	–2.954 to 0.650	0.210
Ethnicity (black vs white)	0.245	–3.722 to 4.212	0.904
Ethnicity (other vs white)	0.253	–4.542 to 5.049	0.918
Widowed/separated/divorced vs married/cohabiting	–0.062	–2.113 to 1.990	0.953
Single vs married/cohabiting	1.496	–0.375 to 3.368	0.117
Duration of symptoms	0.004	–0.005 to 0.012	0.386
Baseline BSI score	0.168	0.059 to 0.276	0.002
Perceived cause: physical vs other	–0.281	–2.304 to 1.741	0.785
Previous anti-depressant treatment (yes vs no)	0.474	–1.167 to 2.115	0.572
Alcohol use (AUDIT score)	–0.006	–0.241 to 0.230	0.962
LEDS severe interpersonal difficulty at baseline	1.205	–0.448 to 5.859	0.153

AUDIT, Alcohol Use Disorders Identification Test; BSI, Bradford Somatic Inventory; LEDS, Life Events and Difficulties Scale.

No interactions between treatment arm and the other predictors included in the model above were found to be significant ($p = 0.909$ for the interaction between treatment arm and age, $p = 0.499$ for that between treatment arm and employment status, and $p = 0.369$ for that between treatment arm and baseline somatic symptom score). Thus, there was no evidence for a differential response to treatment with an SSRI in addition to supportive care for any of these predictors.

TABLE 41 *Longitudinal analysis of potential predictors of HDRS scores at 12 and 26 weeks follow-up, including missingness predictors, after backward selection*

Variable	Coefficient	95% CI	*p*-value
Treatment arm	–1.907	–3.226 to –0.589	0.005
Baseline HDRS score	0.549	0.226 to 0.872	0.001
London vs Southampton	1.134	–0.654 to 2.922	0.214
Liverpool vs Southampton	0.903	–0.822 to 2.627	0.305
Time	–1.104	–1.773 to –0.436	0.001
Age at randomisation	0.023	–0.024 to 0.071	0.340
Employment status (unemployed vs employed)	–1.940	–3.349 to –0.531	0.007
Baseline BSI score	0.164	0.072 to 0.256	< 0.001

Predictors of remission

The overall odds ratio (OR) for remission to HDRS < 8 for intervention versus control, after controlling for centre, baseline level of HDRS, age and employment and clustering for GP, was 2.306 (95% CI 1.194 to 4.453, $p = 0.013$) at 12 weeks and 2.224 (95% CI 1.100 to 4.497, $p = 0.026$) at 26 weeks. The ORs for the mild and moderate subgroups were 1.591 and 3.492 at 12 weeks and 1.623 and 3.148 at 26 weeks. The interaction between arm and severity was not significant at either time point ($p = 0.328$ and $p = 0.298$ respectively). Logistic models were fitted for remission (HDRS < 8) at follow-up with the variables discussed above as potential predictors. Very similar results, in terms of which variables were predictive, were found.

Further predictor analysis including the effect of compliance and blindness

It is anticipated that a more detailed analysis of predictors will be reported in a subsequent publication. Preliminary results are as follows: compliers are defined as those who take at least 28 days of SSRI medication in the treatment group [63 (56%) in the intervention group] and those who take less than this amount or none in the control group [92 (85%)]. Comparing the HDRS totals by arm (using the same longitudinal model as for the intention-to-treat analysis reported above, i.e. controlling for baseline level, centre, age and employment) for the compliers subgroup gives an estimated effect in favour of SSRI treatment of –1.937 (95% CI –3.538 to –0.336, $p = 0.018$).

With regard to the unblinding of researchers, a longitudinal analysis of the interviewer-blinded and unblinded groups gives estimates of the differences between arms of –1.032 (95% CI –2.532 to 0.469, $p = 0.178$) for blinded cases and –4.757 (95% CI –7.342 to –2.171, $p < 0.001$) for unblinded cases. Further analysis, however, suggests that this does not reflect interviewer bias but rather a complex effect due to non-compliance. There are two reasons for this. First, a parallel analysis of the BDI total shows a similar difference between blinded and unblinded cases [blinded –0.841 (95% CI –3.253 to 1.571, $p = 0.494$); unblinded –2.866 (95% CI –6.821 to 1.090, $p = 0.156$)]. This finding for the BDI is not consistent with interviewer bias as an explanation as it is patient completed. For the SF-36 MH scale (also patient completed), the estimates are blinded 1.98 (95% CI –3.812 to 7.773, $p = 0.503$) and unblinded 16.86 (95% CI 8.613 to 25.10, $p < 0.001$). Second, compliance and blindness of researchers are linked: researchers tended to be unblinded more often than the average for those patients who had been prescribed antidepressants contrary to randomisation, i.e. non-compliers in the control group (61% of patients in this subgroup revealed their arm to researchers at 12 weeks compared with an average of 25% at 12 weeks).

Thus, this apparent association with 'blindness' is likely to reflect a more complex treatment and/or compliance effect to do with the patients, rather than the interviewer. Interpretation of treatment effects in the presence of non-compliance and any independent effect of randomisation itself (given that the patients are all unblinded) will depend on a causal model that can take account of all these factors simultaneously and, specifically, the initial level of severity, the dosage of medication actually received and other individual characteristics of compliers and non-compliers. This will be the subject of further analysis.

Process of care

Number of consultations

The aim was for patients in both arms to be seen by the treating GPs four times, at 2, 4, 8 and 12 weeks after randomisation, and the numbers of consultations reported by the patients on the CSRI questionnaire within the first 12 weeks were as follows: in the supportive care alone arm 100 patients (93%) reported subsequent consultations, with a mean of 3.8 (SD 2.0); in the SSRI plus supportive care arm 108 (96%) reported subsequent consultations, with a mean of 4.1 (SD 2.2).

Treatment with SSRIs

Data on the prescriptions for SSRIs given to participating patients were gathered from their medical records after the end of the 26-week follow-up period. *Table 42* shows the number of tablets prescribed to patients.

It is important to note that the numbers of tablets prescribed does not necessarily correspond exactly with the number of days of treatment given, as some SSRIs are given more frequently than once daily, some patients would have stopped treatment and restarted after a gap, and some of the prescriptions given towards the end of the 26 weeks would have been for periods continuing for some

TABLE 42 *Number of SSRI tablets prescribed, according to the GP records, by trial arm*

	Number of patients	
Number of tablets prescribed	**Supportive care alone [*n* (%)]**	**Supportive care plus SSRI [*n* (%)]**
0	83 (76.9)	15 (13.4)
1–30	9 (8.3)	24 (21.4)
31–60	3 (2.8)	9 (8.0)
61–90	1 (0.9)	5 (4.5)
91–120	2 (1.9)	10 (8.9)
121–150	2 (1.9)	12 (10.7)
151–180	1 (0.9)	6 (5.4)
> 180	7 (6.5)	31 (27.7)
Total number of patients	108	112

time beyond the follow-up period. More detailed analysis of the dates of prescriptions and length in days of each prescription for each individual patient is being carried out to determine the mean and range of length of SSRI treatment in days and will be reported in a subsequent publication. According to the CSRI data, the mean duration of SSRI treatment was 144 days, and two-thirds of participants prescribed SSRIs reported using them for the whole of the 26-week period. However, the

TABLE 43 *Side effects of SSRI antidepressants reported by patients at the 12-week follow-up*

	Number of times reported by patients	
Reported side effects of antidepressants taken at 12 weeks	**Supportive care alone**	**SSRI plus supportive care**
Gastrointestinal symptoms	4	21
Tiredness/drowsiness/reduced energy	1	9
Itching/irritation/tingling of skin/rash	1	8
Headache	3	6
Reduced libido	0	5
Anxiety/agitation/mood swings	2	4
Tremor/shaking	1	4
Spaced-out/distant/drunk feeling	0	4
Loss of appetite/weight loss	2	3
Flushing/sweating	1	3
Dry mouth	0	3
Dizziness	0	3
Reduced sleep	1	2
Feeling of carelessness	1	1
Increased appetite/weight gain	0	1
Lump in throat	0	1
Light sensitivity	0	1
Dreaming	0	1
Blackout (memory loss) with alcohol	0	1
Total	17	81

medical record data are likely to be more accurate, as the patients were being asked to recall drug use over the previous 26 weeks. During the 12 weeks following randomisation, of those prescribed SSRIs (across both arms): citalopram was received by 20 (16.4%), escitalopram 11 (9.0%), fluoxetine 89 (73.0%), paroxetine 4 (3.3%) and sertraline 4 (3.3%). The distribution was similar for the following 3-month period: citalopram 14 (19.4%), escitalopram 8 (11.1%), fluoxetine 47 (65.3%), paroxetine 3 (4.2%) and sertraline 3 (4.2%). (These percentages do not sum to 100% due to some patients receiving more than one type of SSRI during the follow-up periods.)

Side effects of SSRI medication reported by the patients

At the 12-week follow-up, adverse effects of antidepressants were reported by 47 patients, of whom 37 who were randomised to the SSRI plus supportive care arm and 10 to the supportive care alone arm (patients in this arm could be prescribed antidepressants at the discretion of the GP if they were thought to be getting worse and in need of medication). All the antidepressants taken were SSRIs.

Table 43 shows the number and type of side effects reported by patients who took SSRIs during the first 12 weeks of the study in each arm, in descending order of frequency of occurrence in the SSRI plus supportive care arm. At the 26-week time point, 42 patients reported side effects, of whom 36 were randomised to the intervention arm and six to the control arm.

Table 44 shows the number and type of side effects reported at 26 weeks by patients who took SSRIs in each arm.

TABLE 44 *Side effects of SSRI antidepressants reported by patients at the 26-week follow-up*

Reported side effects of antidepressants taken at 26 weeks	Number of times reported by patients	
	Supportive care alone	SSRI plus supportive care
Gastrointestinal symptoms	4	19
Flushing/sweating	1	6
Itching/irritation of skin/rash	0	4
Tiredness	1	3
Tremor/shaking	0	3
Dizziness	0	3
Poor concentration/forgetful	0	3
Cramps/painful limbs/muscle spasms	0	3
Loss of appetite/weight loss	0	2
Headache	1	1
Spaced-out feeling	1	1
Reduced sleep	1	1
Dreaming	1	1
Reduced libido	0	1
Dry mouth	0	1
Yawning	0	1
Flashing lights	0	1
Breathlessness	0	1
Feeling low	0	1
Anxiety	1	0
Total	11	56

Adverse events reported by the participating GPs

A total of nine adverse events were reported by the GPs (see Appendix 23). They included four events thought to be adverse reactions to the SSRI medication and seven severe adverse events (two in the supportive care alone arm). There were no suspected unexpected severe adverse reactions.

Patient-reported consultation content

The 10-item PSAC questionnaire, measuring the number of reported consultation content items specific to depression, was completed by 183 of 186 patients followed up at 12 weeks (94 of 96 in the SSRI plus supportive care arm and 89 of 90 in the supportive care alone arm), and by 164 of 167 patients at 26 weeks (89 of 90 in the SSRI plus supportive care arm and 75 of 77 in the supportive care alone arm). The overall mean number of items reported was 8.04 (SD 4.4) and the observed values ranged from 0 to 20. The PSAC score did not differ significantly between the two arms of the study [mean score in SSRI plus supportive care arm 8.2 (SD 4.4) compared with 7.8 (4.5) in the supportive care alone arm, $p = 0.52$]. Thus there was no evidence of a substantial difference in depression-specific consultation content between the study arms. These data will be analysed further and may appear in a subsequent publication.

Chapter 5
Economic evaluation

The economic evaluation was a key component of the THREAD study and involved the following stages:

1. measurement of service use prior to baseline assessment and 26-week follow-up
2. calculation of service costs for each time period
3. comparison of service use and service costs between the two groups (supportive care alone and SSRI plus supportive care)
4. comparisons of cost-effectiveness and cost–utility
5. assessment of impact of interventions on informal care and lost employment.

Service use

Service use during the 6-month periods leading up to the baseline assessment and 26-week follow-up was measured with an adapted version of the CSRI. Services included those provided in the primary care setting (face-to-face GP consultations, GP telephone contacts, practice nurse contacts), secondary care services (inpatient, outpatient, day patient, accident and emergency), community health services (e.g. health visitors, district nurses, counselling or psychological therapists) and social care services (e.g. social workers, housing workers). The CSRI asked patients to state whether they had used specific services, how many contacts they had received and – where relevant – the average duration of service contact (i.e. across all contacts the individual made with each service). Informal care provided by family members and friends was recorded, by asking patients how much extra help (measured in hours per week) they had received specifically because of their health problems. This time was broken down into personal care, childcare, help in the home and help outside the home. The CSRI recorded use of medication for mental health and physical health reasons. The names of medications were recorded along with doses, frequency and duration of use. In addition to service use, the CSRI recorded employment status and interruptions to work as a result of health problems (absenteeism).

The CSRI was not applied at the 12-week follow-up because there were concerns that the information contained within it would 'unblind' the researchers conducting the HDRS interviews. Therefore, the CSRI used at 26 weeks was adapted to include questions on the number of service contacts that were received during the previous 3 months, so that the use up to 12 weeks from baseline could be identified as well as that in the 3 months before the 26-week follow-up.

Combining CSRI data and GP record data

CSRI data were augmented with data collected from general practice computerised medical records. These covered a range of services, and for the purposes of the economic evaluation data we used data on GP consultations (surgery, telephone or home visits), practice nurse contacts and prescriptions of mental health medications (specifically antidepressants, anxiolytics and hypnotics). This was the main data source for mental health problem prescribing, while information on drugs for physical health problems was taken from the CSRI. Regarding GP and practice nurse contacts, a comparison between the CSRI and medical record information was made and the source recording the highest level of contact was used (which would differ by patient).

Service use data are summarised in *Table 45*. In the 6 months before baseline assessment, all patients had GP contacts, which occurred approximately every 6 weeks on average. Slightly less than half also had contacts with practice nurses. More than half were receiving medication for physical health problems, and around one-third had outpatient contacts during the 6 months prior to baseline, which indicates a considerable level of physical health comorbidity in the trial population, as might be expected in a population selected on the basis of having somatic symptoms. A small number of patients (three in the supportive care alone group and one in the SSRI plus supportive care group) were prescribed SSRIs during the 6 months prior to baseline. However, records indicated that none of these four prescriptions was 'cashed'. Most other services were used by relatively few patients. Overall, there were few noticeable differences between the two groups at baseline, although the

TABLE 45 *Number of patients using services and mean number of contacts before baseline assessment, 12-week follow-up and 26-week follow-up*

	6 months to baseline				Baseline to 12-week follow-up				Baseline to 26-week follow-up			
	Supportive care alone		SSRI plus supportive care		Supportive care alone		SSRI plus supportive care		Supportive care alone		SSRI plus supportive care	
Service	***n* (%)**	**Mean (SD)[a]**	***n* (%)**	**Mean (SD)[a]**	***n* (%)**	**Mean (SD)[a]**	***n* (%)**	**Mean (SD)[a]**	***n* (%)**	**Mean (SD)[a]**	***n* (%)**	**Mean (SD)[a]**
Inpatient admission[b]	9 (9)	2.2 (2.2)	6 (5)	1.8 (1.3)	2 (3)	7.5 (9.2)	3 (4)	3.7 (3.1)	2 (3)	9.0 (7.1)	5 (6)	8.4 (11.8)
Outpatient consultation	41 (39)	2.9 (2.6)	37 (33)	2.4 (1.7)	17 (23)	2.1 (2.2)	19 (22)	1.8 (1.3)	24 (32)	2.7 (2.3)	28 (33)	2.3 (2.1)
Day patient admission	3 (3)	3.7 (3.8)	2 (2)	1.0 (0.0)	1 (1)	1.0 (–)	1 (1)	1.0 (–)	1 (1)	1.0 (–)	1 (1)	1.0 (–)
A&E consultation	10 (9)	1.4 (0.7)	12 (11)	1.2 (0.4)	3 (4)	3.0 (1.4)	4 (5)	1.8 (1.5)	4 (5)	3.3 (3.9)	7 (8)	3.4 (3.6)
GP surgery consultation	108 (100)	4.1 (2.9)	112 (100)	4.4 (2.6)	100 (93)	3.8 (2.0)	108 (96)	4.1 (2.2)	105 (97)	5.5 (3.1)	109 (97)	6.5 (3.2)
GP telephone contact	26 (24)	1.3 (0.8)	13 (12)	1.8 (1.2)	21 (19)	1.2 (0.5)	27 (24)	1.1 (0.3)	31 (29)	1.5 (0.8)	32 (29)	1.3 (0.6)
GP home visit	3 (3)	1.3 (0.6)	0 (0)	–	3 (3)	1.7 (1.2)	3 (3)	2.7 (2.9)	6 (6)	1.3 (0.8)	5 (5)	2.0 (2.2)
Practice nurse contact	48 (44)	1.9 (1.4)	55 (49)	1.7 (1.2)	23 (21)	1.4 (0.9)	26 (23)	1.4 (0.9)	38 (35)	1.7 (1.5)	37 (33)	2.0 (2.0)
District nurse contact	0 (0)	–	1 (1)	4.0 (–)	0 (0)	–	1 (1)	1.0 (–)	0 (0)	–	1 (1)	1.0 (–)
Community mental health nurse contact	1 (1)	3.0 (–)	0 (0)	–	1 (1)	4.0 (–)	2 (2)	1.0 (–)	1 (1)	4.0 (–)	2 (2)	1.0 (0.0)
Other nurse contact	2 (2)	5.5 (6.4)	5 (5)	2.4 (2.6)	0 (0)	–	3 (4)	1.5 (0.7)	1 (1)	1.0 (–)	3 (4)	1.7 (0.6)
Health visitor contact	9 (9)	4.9 (5.3)	8 (7)	1.5 (0.5)	2 (3)	1.0 (0.0)	0 (0)	–	2 (3)	1.5 (0.7)	1 (1)	3.0 (–)
Counsellor contact	7 (7)	2.0 (1.0)	9 (8)	3.2 (2.2)	12 (16)	3.6 (3.5)	11 (13)	5.1 (2.8)	15 (20)	6.3 (4.7)	13 (15)	6.1 (3.3)
Complementary health care	9 (9)	5.9 (4.9)	5 (5)	2.0 (1.4)	5 (7)	5.0 (4.3)	3 (4)	1.7 (1.6)	7 (10)	7.4 (6.6)	6 (7)	2.5 (2.5)
Psychologist contact	1 (1)	3.0 (–)	0 (0)	–	2 (3)	7.5 (9.2)	3 (4)	1.0 (–)	3 (4)	9.3 (14.4)	3 (4)	2.0 (1.0)
Occupational therapist	2 (2)	2.0 (1.4)	2 (2)	1.5 (0.7)	0 (0)	–	4 (5)	1.5 (0.7)	0 (0)	–	6 (7)	1.8 (1.0)
Social worker contact	1 (1)	1.0 (–)	1 (1)	12.0 (–)	1 (1)	2.0 (–)	0 (0)	–	1 (1)	5.0 (–)	0 (0)	–
Housing worker contact	3 (3)	2.7 (2.9)	4 (4)	2.3 (1.0)	0 (0)	–	3 (4)	1.0 (0.0)	2 (3)	1.0 (0.0)	4 (5)	2.0 (1.2)
Community support worker	1 (1)	–	0 (0)	–	1 (1)	12.0 (–)	2 (2)	4.3 (4.6)	1 (1)	24.0 (–)	2 (2)	8.0 (9.9)
Day centre attendance	3 (3)	15.0 (12.3)	1 (1)	3.0 (–)	2 (3)	3.0 (–)	0 (0)	–	2 (3)	6.0 (–)	1 (1)	3.0 (–)
Other services	10 (9)	–	6 (6)	–	3 (4)	–	8 (9)	–	4 (5)	–	11 (13)	–
Medication (physical)	57 (54)	–	67 (62)	–	–	–	–	–	44 (59)	–	54 (61)	–
Medication (SSRIs)	3 (3)	–	1 (1)	–	22 (20)	–	97 (87)	–	25 (23)	–	97 (87)	–
Medication (other mental health)	12 (11)	–	15 (13)	–	21 (19)	–	13 (12)	–	23 (21)	–	17 (15)	–

a Number of contacts is just for those using each service (i.e. not the whole sample).
b Contacts represent number of inpatient days.

group randomised to supportive care alone did have a higher rate of GP telephone contacts.

During the period between baseline assessment and 12-week follow-up, the vast majority of patients again had contact with GPs. (The few for whom no contacts were recorded had also dropped out of the study.) There was a reduction in contacts with practice nurses and outpatient consultations compared with baseline. The number of prescriptions of psychotropic drugs other than SSRIs remained similar to baseline. (Drugs for physical health problems were recorded with the CSRI but these data were not separated into the two follow-up periods.) The only key difference was in the use of SSRIs, which, not surprisingly, was higher in the SSRI plus supportive care group. However, it is important to note that 13% of patients in the SSRI plus supportive care group were not prescribed an SSRI, while 20% of patients in the supportive care alone group were prescribed one.

Between baseline assessment and the 26-week follow-up, slightly more patients in the SSRI plus supportive care group were admitted to hospital, but overall the numbers in each group were small at 4–7% (including day care). Again, one-third of patients had used outpatient services. Prescriptions for physical health problems continued to be received by more than half of the sample. As before, differences between the samples were small with the exception of the prescription of SSRIs. Therefore, there appeared to be no evidence that the intervention was reducing the reliance on other services. (Informal care costs are discussed later, alongside the costs of lost employment.)

Service costs

Service use data were combined with information on unit costs obtained from recognised sources. Most unit costs were taken from the annual publication of the Personal Social Services Research Unit (University of Kent).[75] These costs reflect salaries, overheads and capital, and are divided by the amount of face-to-face time that professionals spend with patients. Medication costs were derived from the *British National Formulary* for September 2007, assuming generic prescribing.[76] Finally, NHS reference costs were used to cost the use of hospital-based services.[77] The unit costs used in the cost calculations are shown in Appendix 24. The year used for unit costs was 2006–7, with the exception of the hospital costs, which were based on the most recently available data, for 2005–6, but inflated to estimate costs in 2006–7.

At baseline, mean costs were highest for GP surgery consultations, outpatient contacts and inpatient episodes (*Table 46*). Inpatient and outpatient costs were higher for the supportive care alone group, as were the costs of complementary health care and community support workers. The cost of medication for physical health problems was higher for the SSRI plus supportive care group. However, the variation around the means was substantial, as indicated by the SDs.

In the 12 weeks after randomisation, the use of inpatient and outpatient care and GP surgery consultations again incurred the highest costs. There were few substantial cost differences between the two groups, with the exception of the SSRI costs. Over the entire 26-week follow-up, the SSRI plus supportive care group had inpatient costs that were double those for the supportive care alone group. This group also had higher GP surgery consultation costs and SSRI costs.

Mean service costs in the 6 months to baseline were £94 higher in the supportive care alone group than in the SSRI plus supportive care group (*Table 47*). Costs up to the 12-week follow-up were closely matched between the groups, and the difference adjusted for baseline was £28. The 95% CI shows this to be non-significant. (Owing to cost data being skewed, bootstrapping with 10,000 resamples was used to produce percentile CIs. This assumes that the distribution of the original sample is representative of the population from which it is drawn. However, calculation of the CIs is the same, regardless of the nature of this distribution.) However, by the 26-week follow-up the mean costs for the SSRI plus supportive care group were £153 higher than for the supportive care alone group, after adjusting for differences in baseline costs. However, the SDs were large and this difference was also non-significant.

Incremental cost-effectiveness ratios

Service costs were linked with the HDRS to assess cost-effectiveness at 12 weeks and 26 weeks. Chapter 4 has shown that at the 12-week follow-up the mean fall in HDRS score for the SSRI plus supportive care group was 2.3 points greater than the fall for the supportive care alone group. Therefore, the SSRI plus supportive care group

TABLE 46 *Mean (SD)[a] service costs 2006–7 (£)*

Service	6 months to baseline		Baseline to 12-week follow-up		Baseline to 26-week follow-up	
	Supportive care alone	SSRI plus supportive care	Supportive care alone	SSRI plus supportive care	Supportive care alone	SSRI plus supportive care
Inpatient admission[b]	93 (431)	49 (248)	100 (804)	63 (406)	120 (831)	241 (1593)
Outpatient consultation	96 (183)	67 (125)	40 (112)	31 (77)	75 (155)	63 (135)
Day patient admission	13 (99)	2 (16)	2 (14)	1 (13)	2 (14)	1 (13)
A&E consultation	11 (39)	11 (32)	7 (44)	7 (39)	15 (90)	23 (112)
GP surgery consultation	124 (86)	133 (77)	104 (65)	118 (69)	161 (96)	190 (101)
GP telephone contact	6 (12)	4 (12)	4 (10)	5 (9)	8 (14)	7 (12)
GP home visit	2 (11)	0 (0)	2 (16)	4 (28)	4 (17)	4 (29)
Practice nurse contact	8 (13)	8 (12)	3 (7)	3 (7)	6 (12)	7 (15)
District nurse contact	0 (0)	1 (8)	0 (0)	< 1 (2)	0 (0)	< 1 (2)
Community mental health nurse contact	3 (28)	0 (0)	3 (22)	< 1 (3)	3 (22)	1 (5)
Other nurse contact	1 (9)	1 (13)	0 (0)	< 1 (2)	< 1 (2)	1 (3)
Health visitor contact	13 (68)	3 (14)	< 1 (2)	0 (0)	< 1 (3)	< 1 (2)
Counsellor contact	5 (20)	8 (31)	20 (67)	18 (58)	34 (99)	32 (90)
Complementary health care	11 (51)	3 (22)	11 (51)	2 (14)	24 (93)	6 (31)
Psychologist contact	2 (20)	0 (0)	11 (91)	2 (11)	21 (169)	5 (27)
Occupational therapist	1 (5)	< 1 (1)	0 (0)	2 (8)	0 (0)	3 (15)
Social worker contact	1 (12)	27 (287)	3 (29)	0 (0)	9 (73)	0 (0)
Housing worker contact	8 (73)	5 (37)	0 (0)	1 (7)	1 (6)	5 (31)
Community support worker	16 (163)	0 (0)	6 (49)	13 (113)	11 (98)	25 (226)
Day centre attendance	10 (71)	1 (7)	2 (12)	0 (0)	4 (23)	1 (8)
Other services	14 (86)	4 (19)	5 (39)	8 (39)	5 (39)	17 (82)
Medication (physical)	75 (220)	91 (250)	49 (147)	55 (141)	99 (295)	110 (282)
Medication (SSRIs)	0.1 (0.4)	0.01 (0.14)	2 (7)	7 (13)	5 (21)	13 (26)
Medication (other mental health)	0.3 (1)	1 (4)	3 (11)	1 (5)	6 (24)	2 (14)

a Number of contacts is just for those using each service (i.e. not the whole sample).
b Contacts represent number of inpatient days.

TABLE 47 *Total mean (SD) service costs 2006–7 (£)*

	Supportive care alone	SSRI plus supportive care	Difference adjusted for baseline and 95% CI
6 months to baseline	513 (659)	419 (547)	–
Baseline to 12-week follow-up	388 (932)	341 (454)	–28 (–656 to 117)
Baseline to 26-week follow-up	629 (1092)	759 (1730)	153 (–500 to 304)

had a better outcome and lower costs and may be described as 'dominant'. At 26 weeks, the mean fall in HDRS scores was 1.7 points greater in the SSRI plus supportive care group. Given that this group also had a cost that was £153 higher than the supportive care alone group, it was necessary to compute an ICER to assist decision makers in assessing whether adding SSRIs to supportive care represents value for money. An ICER is defined as the difference in costs between two groups divided by the difference in outcomes. At 26 weeks, the ICER is therefore £153 divided by 1.7, i.e. £90. This is the extra cost incurred by the SSRI plus supportive care group in achieving an extra unit of improvement on the HDRS compared with the supportive care alone group.

Cost-effectiveness planes

The above calculations of dominance at 12 weeks and an ICER of £90 at 26 weeks are based on the average cost and HDRS differences and therefore do not take uncertainty around these estimates into account. To address such uncertainty, cost-effectiveness planes were produced to show the probability of the SSRI plus supportive care group having (1) lower costs and better outcomes, (2) higher costs and better outcomes, (3) lower costs and worse outcomes and (4) higher costs and worse outcomes in comparison with supportive care alone. To construct the cost-effectiveness planes, four regression models were run using 1000 bootstrapped resamples. The models used service costs and HDRS scores at 12 weeks and 26 weeks as the dependent variables. The independent variables were the group identifier and the baseline measure of cost or HDRS. The 1000 coefficients for the group identifier variable are 1000 estimates of the cost/outcome differences and these were plotted against each other.

The cost-effectiveness plane showing cost and HDRS differences at 12 weeks is shown in *Figure 7*. The 'south-east' quadrant indicates the situation where the SSRI plus supportive care group has lower costs and better outcome than the supportive care alone group, and 54.9% of resamples showed this result. By contrast, 45.0% of cost–outcome differences were in the 'north-east' quadrant, where the SSRI plus supportive care group has better outcomes but also higher costs. Only 0.1% of resamples showed the SSRI plus supportive care group having lower costs and worse outcomes ('south-west' quadrant) and none showed higher costs and worse outcomes ('north-west' quadrant).

At the 26-week follow-up, the majority (76.7%) of resamples showed that the SSRI plus supportive care group had higher costs and better outcomes (*Figure 8*). In 22.2% of resamples there were lower costs and better outcomes, while 0.8% of resamples

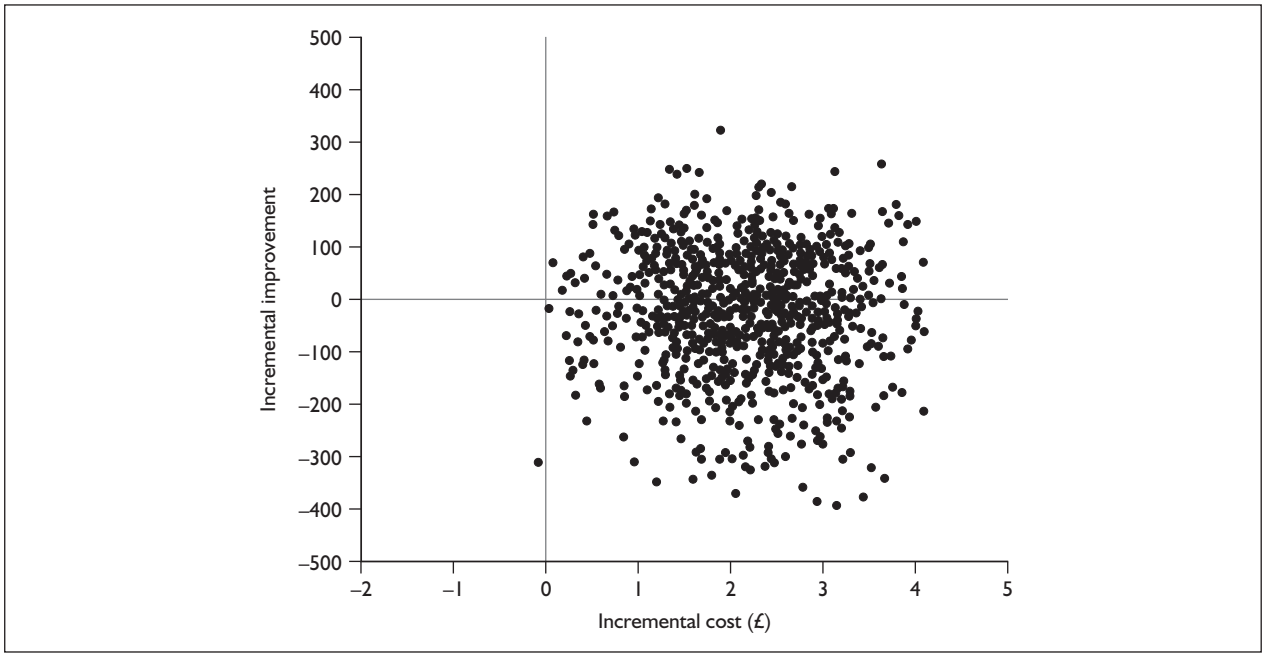

FIGURE 7 *Cost-effectiveness plane of cost and HDRS differences at 12 weeks.*

showed higher costs and worse outcomes. Finally, 0.3% of resamples showed the SSRI plus supportive care group to have lower costs and worse outcomes.

At both 12 weeks and 26 weeks, there was a high likelihood of the SSRI plus supportive care group having higher costs and better outcomes as measured by the HDRS. Whether this incremental improvement in outcome represents good value for money given the likelihood of higher service costs is a value judgement. However, this judgement can be informed by constructing CEACs, which show the likelihood that adding SSRIs to supportive care is more cost-effective than supportive care alone for different values placed on a unit improvement on the HDRS.

Cost-effectiveness acceptability curves

CEACs were constructed using the net-benefit approach.[5] There is a theoretical, but unknown, value (represented by the term λ) that society would place on a one-unit reduction in depression as measured by the HDRS. Net benefit can be defined as:

$$NB = (\lambda \times E) - SC$$

where NB = net benefit, E = effectiveness (i.e. reduction in the HDRS score over 12 and 26 weeks compared with baseline) and SC = service costs. For example, if, for a particular patient, the HDRS score is reduced by 8 points during the follow-up period and if their service cost is £250, then we can calculate their net benefit if we know λ. If λ = £0, then the net benefit is –£250, whereas if λ = £40, then the net benefit is £70. Net benefits for all patients were estimated by assuming different values for λ, ranging between £0 and £200 in £20 increments. Then a regression model was used to determine the mean difference in net benefit between the supportive care alone and SSRI plus supportive care groups for every value of λ. For each model, 1000 regression coefficients for the group identifier variable were generated using bootstrapping, and the proportion of these that were greater than 0 indicated the probability that SSRI plus supportive care was more cost-effective (i.e. it resulted in a mean incremental net benefit greater than 0). These probabilities were subsequently used to generate the CEACs.

The 12-week and 26-week CEACs are shown in *Figure 9*. With regard to the 12-week curve, even if society would not be willing to attach any monetary value to a one-unit reduction in the HDRS there would remain a likelihood of 55% that SSRIs plus supportive care is the most cost-effective option. As a unit improvement is valued at higher levels, this likelihood goes on increasing. While we do not know the true societal value that should be placed on a unit improvement on the HDRS, it

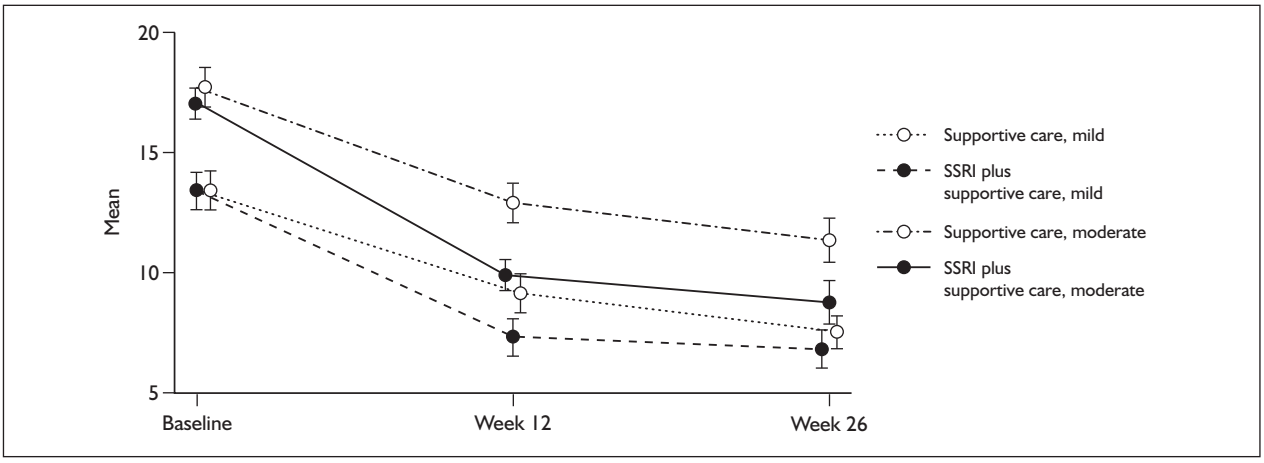

FIGURE 8 *Cost-effectiveness plane of cost and HDRS differences at 26 weeks.*

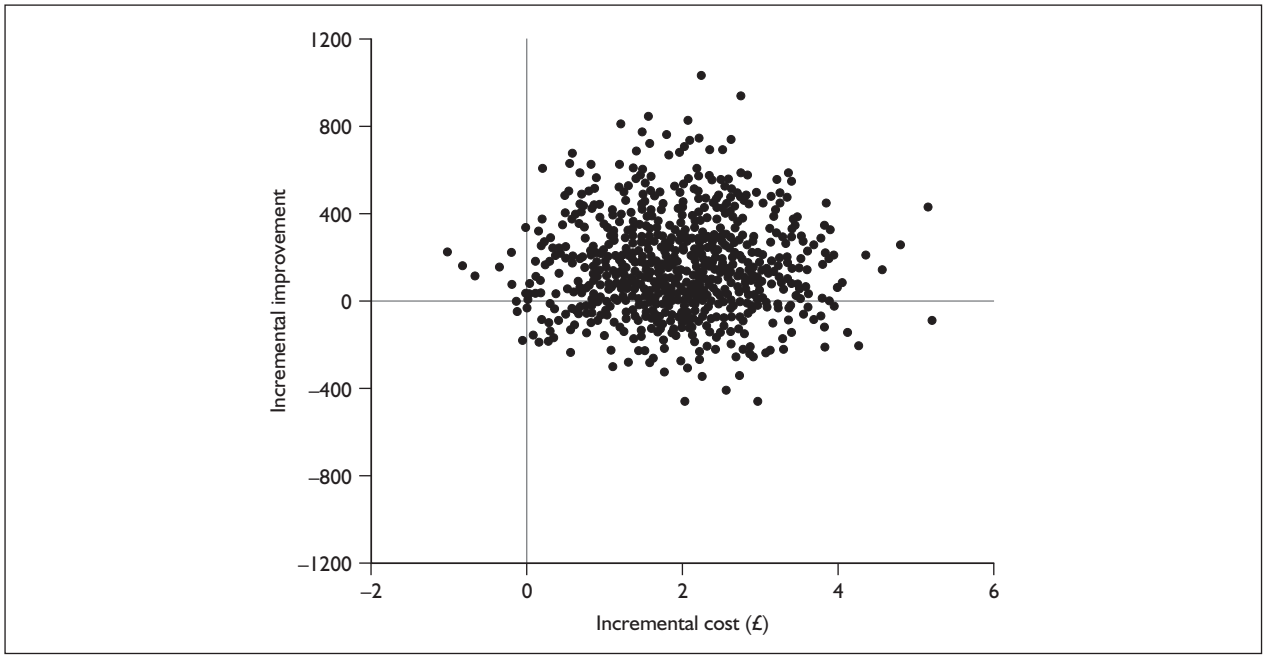

FIGURE 9 *Cost-effectiveness acceptability curves showing probability that SSRIs plus supportive care is most cost-effective option.*

can be seen that beyond around £100 the curve flattens out, meaning that further increases have a diminishing impact on the likelihood that adding an SSRI will be the most cost-effective option.

The 26-week CEAC is below the 12-week CEAC, which reflects the reduced difference between the two groups at 26 weeks and the higher cost for the SSRI plus supportive care group. The latter intervention has a greater than 50% likelihood of being the most cost-effective option only if the value placed on a unit reduction on the HDRS is above £80.

Cost–utility analysis

Measuring outcomes using the HDRS has obvious clinical relevance and allows the results of this study to be compared with those of many other depression trials. However, policy makers need to make decisions regarding interventions across all areas of health care, and therefore a generic measure of outcome is also required. The most commonly used generic measure is the QALY, where the time spent in a health state is adjusted by a figure between 0 and 1 to reflect quality of life. This 'utility' value was generated from the SF-36 using an algorithm developed by Brazier and colleagues.[78] Clearly, there are other ways of estimating QALYs, and indeed alternative algorithms for calculating utility scores do exist. These may have produced different findings. However, the Brazier *et al*. method seemed most appropriate because it was based on the SF-36 (rather than the SF-12, as used elsewhere) and on a UK sample. The utility scores at baseline assessment and each follow-up are shown in *Table 48*. Scores at 12-week follow-up were significantly higher in the SSRI plus supportive care group. At 26-weeks the difference was non-significant.

Calculation of quality-adjusted life-years

Quality-adjusted life-years were calculated using area under the curve methodology.[79] The baseline

TABLE 48 *Mean (SD) utility scores at baseline assessment, 12-week, and 26-week follow-up*

	Supportive care alone	SSRI plus supportive care	Difference adjusted for baseline (95% CI)
6 months to baseline	0.5748 (0.0714)	0.5857 (0.0700)	–
Baseline to 12-week follow-up	0.6467 (0.1230)	0.6856 (0.1237)	0.0360 (0.0005 to 0.0715)
Baseline to 26-week follow-up	0.6782 (0.1339)	0.6998 (0.1295)	0.0175 (–0.0230 to 0.0579)

utility score was added to the score at 12 weeks and this total was divided by 2, based on the assumption of a linear change over the 12-week period. This figure was then multiplied by 0.25, as only one-quarter of a QALY could be gained over the 12-week period. The QALY gain in the 12-week to 26-week period was calculated in a similar way. Gains in QALYs over the entire 26-week follow-up period were calculated by adding these two 3-month QALY gains. The mean QALY gain between baseline and 12-week follow-up was 0.1522 for the supportive care alone group and 0.1588 for the SSRI plus supportive care group. The difference adjusting for baseline was 0.0045 in favour of the SSRI plus supportive care group. As with the HDRS measure, adding SSRIs to supportive care was 'dominant' as costs were lower and QALY gains greater. By 26 weeks, the QALY gain in the supportive care alone group was 0.3176 and in the SSRI plus supportive care group it was 0.3305. The adjusted difference was 0.0103. Dividing the incremental cost of £153 by 0.0103 produced an ICER of £14,854, i.e. a cost of £14,854 would be incurred to gain an extra QALY as a result of prescribing SSRIs along with supportive care.

Uncertainty around the finding of dominance at 12 weeks and the ICER of £14,854 at 26 weeks were explored, as before, using cost-effectiveness planes. At 12 weeks, 52.1% of the resamples showed lower costs and a greater QALY gain for the SSRI plus supportive care group while 44.8% showed higher costs and more QALYs (*Figure 10*). Only 1.0% showed lower costs and a lower QALY gain and 2.1% showed higher costs and a lower QALY gain. The cost-effectiveness plane for the QALY gain and cost differences by 26 weeks is similar to that for the HDRS at 26 weeks (*Figure 11*). Most resamples (72.1%) showed higher costs and a greater QALY gain for the SSRI plus supportive care group. Lower costs and more QALYs were revealed in 24.3% of resamples. Lower costs and fewer QALYs were shown by 0.2% of resamples and higher costs and fewer QALYs by 3.4%.

CEACs were produced using the net-benefit approach as described above. The range of λ values was between £0 and £50,000 in £5000 intervals. (This range was chosen as values above this would usually mean that the intervention would not be recommended by NICE.) *Figure 12* shows that with a zero value attached to a QALY gain at 12 weeks, there is still a 53% likelihood of SSRIs plus supportive care being cost-effective. With a QALY gain valued at £20,000–£30,000 (the thresholds usually associated with NICE recommendations), there is an 80–85% likelihood of this being the most cost-effective option. The CEAC related to QALYs at 26 weeks is again below the 12-week CEAC. However, there remains a high likelihood that SSRIs plus supportive care are cost-effective: 65% to 75% for a value of £20,000 to £30,000 per QALY respectively.

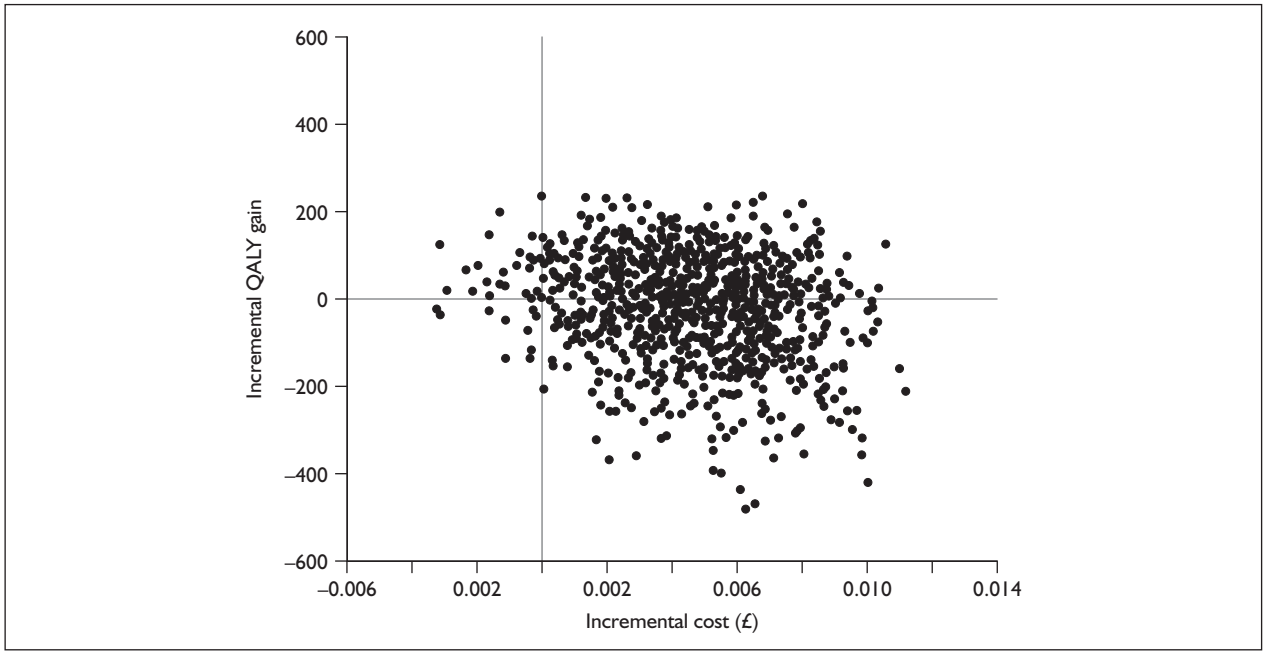

FIGURE 10 *Cost-effectiveness plane of cost and QALY differences at 12 weeks.*

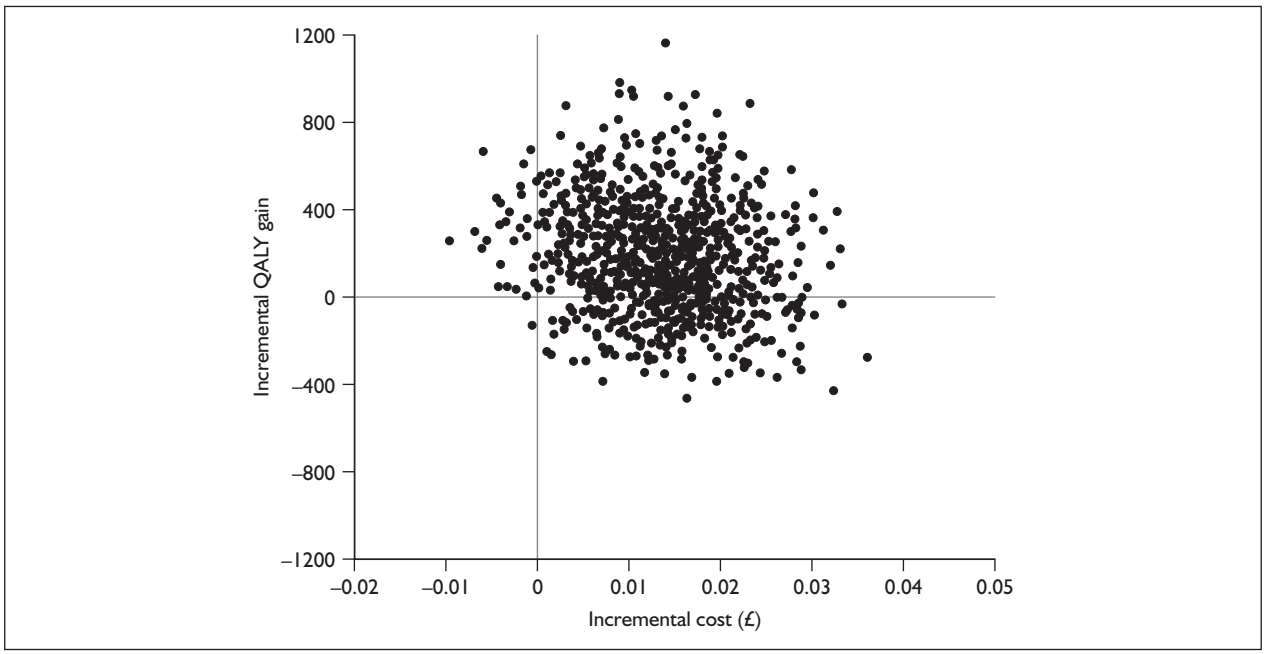

FIGURE 11 *Cost-effectiveness plane of cost and QALY differences at 26 weeks.*

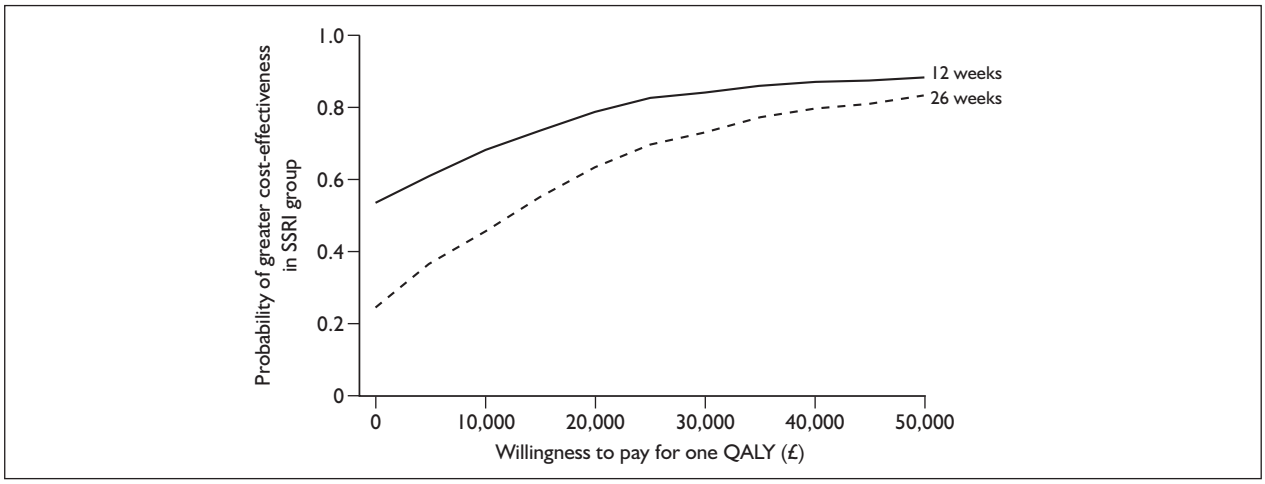

FIGURE 12 *Cost-effectiveness acceptability curves showing probability that SSRIs plus supportive care is most cost-effective option.*

Impact on carers and employment

The above analyses focus on health and social care costs. However, it is likely that people with depression will require help from family members/friends as a result of their condition. In addition, it is well known that depression has a major impact on work. Data on the use and costs of informal care and the impact on work are shown in *Table 49*.

While relatively few patients received informal care, the cost was high. The unit cost used was the hourly cost of a homecare worker, and those who did receive informal care did so for a substantial number of hours per week. It can be seen that informal care costs were greatest for the SSRI plus supportive care group during the follow-up period but that this difference was not statistically significant. The costs of informal care were high, and this may be seen as surprising. For some disorders (e.g. dementia), high levels of informal

TABLE 49 *Use and cost of informal care and impact on employment*

	6 months to baseline		Baseline to 26-week follow-up	
	Supportive care alone	**SSRI plus supportive care**	**Supportive care alone**	**SSRI plus supportive care**
n (%) using informal care	13 (12)	17 (16)	11 (15)	13 (15)
Mean (SD) hours per week[a]	5.2 (5.2)	6.4 (8.7)	4.3 (6.1)	6.5 (9.3)
Mean (SD) cost (£)[b]	267 (1021)	412 (1688)	202 (672)	397 (1744)
n (%) with lost work	14 (13)	14 (13)	11 (15)	18 (22)
Mean (SD) lost weeks[c]	17.6 (11.4)	11.7 (10.7)	19.8 (9.7)	18.3 (10.1)
Mean (SD) production loss (£)[d]	786 (2856)	504 (2128)	1146 (3381)	1484 (3725)

a Hours per week for those receiving informal care.
b Cost across whole sample.
c Lost weeks for those with lost employment.
d Lost production cost for whole sample.

care would be expected, but perhaps not for depression. Informal care costs were not included in the cost-effectiveness analyses because in the UK, NICE generally takes an NHS perspective. However, we have shown that these costs are important and should be investigated further.

Lost employment was experienced by a small number of patients. This could, however, be an underestimate as patients were asked to describe interruptions to work rather than asked specifically for the amount of time off, although many did provide this information. Lost employment costs were, though, substantial if costed at the median wage in the UK in 2007 of £457 per week. These costs increased during the follow-up period but did not differ significantly between the groups. It is interesting, however, that the apparent health improvement for those in the SSRI group was not matched by reductions in lost employment. This may be because (1) receipt of SSRIs 'reinforced' the feeling of being unwell and/or (2) doctors may be more likely to sign a patient off work at the same time as issuing a prescription of antidepressants. As with informal care costs, we did not include lost employment costs in the cost-effectiveness analyses because of the perspective taken by NICE.

Chapter 6
Discussion

Summary of the main findings

Primary and secondary outcomes

Statistically significant differences in favour of the SSRI plus supportive care arm at follow-up were found in terms of lower scores on the HDRS, higher scores on the SF-36 MH subscale and higher scores on the MISS, but not in terms of lower BDI scores. Differences in the SF-36 VT score were of borderline significance, and the other SF-36 subscales were not significantly different.

Significant differences between the arms in the mean fall in HDRS score were found at both follow-up points when analysed separately, but were relatively small: 2.3 points at 12 weeks and 1.7 points at 26 weeks. The NNTs for remission (to HDRS < 8) were 6 at 12 weeks and 6 at 26 weeks, and the NNTs for significant improvement (HDRS fall of $\geq 50\%$) were 7 and 5 respectively. These numbers suggest that the addition of an SSRI is useful clinically, as fewer than eight patients need to be treated for one to gain clinically significant benefit, although these summary figures have to be treated with caution as the CIs around these estimated NNTs were relatively wide.

Predictors of outcome

No significant differences were found between severity subgroups for the HDRS findings in the longitudinal analysis including outcomes at both follow-up points, so we have no evidence of a differential response to treatment between patients with mild and moderate depression in this sample. The mean HDRS scores in the two arms did converge more by 26 weeks in the mild depression subgroup than in the moderate subgroup, but the interaction terms were not significant. However, the study had limited power to determine differences in response between the two severity subgroups (see below).

A poorer outcome in terms of a higher HDRS score at follow-up was significantly related to a higher baseline HDRS score, higher baseline BSI physical symptom score and being unemployed at baseline. It is important to note that the effect size of unemployment was of a similar magnitude to that of the treatment arm. A higher BDI score at follow-up was also significantly related to a higher baseline BDI score and unemployment at baseline. A lower MH score at follow-up was also significantly related to lower baseline values and unemployment at baseline. A lower VT score at follow-up was also significantly related to a lower baseline VT score and older age at randomisation, with a borderline significant relationship to unemployment at baseline.

None of the other possible predictors of outcome was significantly related to the HDRS score at follow-up, including sociodemographic factors, life events and difficulties at baseline, duration of depression, a past history of depression, previous use of antidepressants, a physical versus non-physical patient attribution of symptoms or level of alcohol use. There were also no statistically significant interactions between these possible predictors and trial arm in terms of predicting a differential response to SSRI treatment.

Costs and cost-effectiveness

Costs were slightly higher in the SSRI plus supportive care arm, but not statistically significantly different. Incremental cost-effectiveness ratios and cost-effectiveness planes suggested that adding an SSRI to supportive care is probably cost-effective, with mean costs of £90 per point improvement on the HDRS and £14,854 per QALY gain. The CEAC for utility suggested that adding an SSRI to supportive care is cost-effective at the value of £20,000–£30,000 per QALY used by NICE, with a 65–75% probability. Informal care costs were relatively high, given that the patients had only mild to moderate depression, but did not differ significantly between arms.

The process of care

More than 90% of patients in each arm received supportive care from the GPs, with a mean number of consultations of around four during the 12-week treatment period, as planned. In the event, SSRI antidepressants were received by 87% of patients in the SSRI plus supportive care arm, so

13% were not treated despite being randomised to receive an SSRI. Furthermore, 20% of patients in the supportive care alone arm were also treated with SSRIs, which was permissible within the protocol if, in the GP's clinical judgement, the patient worsened and required drug treatment. No difference was found in patient-reported consultation content between arms, suggesting that GPs do not discuss non-drug strategies to tackle depression to a greater extent with their patients when they are not prescribing an antidepressant.

Strengths of the study

Even though practitioner referral rates into the study were lower than anticipated and one in three patients referred declined to be randomised, the research team managed to achieve the assessment of our primary outcome in 186 patients, close to our target sample size of 196, through the recruitment of more and more practitioners over more than 3 years. This was particularly challenging, owing to a steady stream of adverse publicity in the media about the effects of antidepressants throughout the course of the trial.[80–83] However, as a result of the team's efforts, the study had sufficient power to determine a relatively small difference in outcome between the two arms of around 1.5 points on the HDRS. The randomisation process was also successful, with well balanced numbers in the two arms and in the two severity subgroups within each arm. We achieved higher than expected follow-up rates at both time points, reducing the likelihood of bias due to patients dropping out. Patients were followed up for 26 weeks, which is considerably longer than most commercial drug trials which have only 6–12 weeks' follow-up, and the two follow-up points allowed longitudinal analyses of outcomes, which maximised the power of the sample to detect differences between arms.

A range of relevant primary and secondary outcomes were measured, including depressive symptoms, generic health status, patient satisfaction and costs. Costs were carefully gathered from a health service perspective using both patient questionnaires and GP medical records to maximise completeness,[70] and informal care costs, including interruption of work and costs to family and friends, were also gathered. Most of the assessments carried out were self-completed, avoiding the possibility of observer bias. Interviewer training and frequent inter-rater reliability checks ensured high quality and consistent measurement of the HDRS primary outcome, and greatly reduced the likelihood of observer bias.

Data were collected on patients seen in surgeries who were eligible for the study but were not referred and on patients who were referred but not randomised, which allowed exploration of the representativeness of randomised patients. In addition, reasons for non-participation were gathered from those patients referred to the study team who did not consent to be randomised.

Therefore, in a number of respects, this study compares very favourably with primary care trials of antidepressants identified in a recent systematic review, most of which were small, commercially funded studies of short duration and low methodological quality.[23,84] It is crucial that clinicians working in primary care have good quality evidence from primary care studies to inform their practice. The 2004 NICE guidelines on antidepressant treatment were based on a review including 31 outpatient-based studies, three inpatient studies, 13 mixed studies and only one from primary care.[11] Among the 19 studies for which it was possible to determine baseline severity, four were of moderate depression, six of severe depression and nine of very severe depression.[11] Therefore, there was clearly a need for further, comparable studies of the treatment of mild to moderate depression in primary care.

Limitations of the study

The study was powered to detect only a relatively large difference in outcome, of 2.5 points on the HDRS, between the mild and moderate severity subgroups, and was not powered to detect equivalence in the effect of treatment. Therefore, while we found little evidence of a differential response to treatment between the two severity subgroups, we cannot say that adding an SSRI to supportive care is as effective in mild depression as in moderate depression. The power of the study was even more limited for the analyses of the other possible predictors of outcome and response to treatment, which must be regarded as exploratory.

We allowed GPs to prescribe antidepressants to patients in the supportive care alone arm if their depression persisted or worsened, so the drug treatment of 20% of patients in that arm was not a protocol violation as such. We did not collect any data on why GPs failed to prescribe SSRIs to

13% of the patients randomised to the SSRI plus supportive care arm, although this was probably because the GP and patient between them decided they did not want to use them after all. Qualitative interviews with the participating GPs might have shed light on why they failed to follow the randomisation recommendations in a minority of cases in both arms.

In an open label pragmatic trial of this nature, it is often not possible to keep the researchers responsible for assessing outcome in the patients blind to allocation to trial arm. In this study, the researchers were unblinded in 25% of cases at 12 weeks and 33% at 26 weeks, which raises the possibility of observer bias. In this respect, it is also important to note that we did not see similar changes in the self-completed BDI to the observer-rated changes in the HDRS. However, we consider that observer bias is an unlikely explanation for the effects found on the HDRS, for a number of reasons. First, the careful training and frequent inter-rater reliability checks would have greatly reduced the likelihood of observer bias, as the researchers were taught how to interpret patient responses to the individual items on the HDRS in a consistent way, and they were aware that a random sample of their audiotaped interviews would be rated again by a second researcher and discussed with one of the trainers. Second, we did see corresponding changes to the HDRS findings in the self-completed MH and VT subscales of the SF-36, as well as in self-rated patient satisfaction scores, so the lack of changes in the BDI may have been due to a relative insensitivity to change (see below), rather than because it was self-completed. Third, there was no expectation in the study group either way about the likely outcome which might have biased the researchers towards finding an effect. The study group included investigators holding a range of contrasting views about the effectiveness of antidepressants, and we consciously and explicitly maintained equipoise about the likely findings in discussion in study group meetings, stressing that we were interested in the outcome whatever the result.

We experienced greater loss to follow-up in the London centre than in the other two, which was due partly to a member of the team leaving the study and a gap in the availability of a researcher in London to carry out follow-up assessments for a few months until a replacement could be appointed. There was also differential loss to follow-up between the two treatment arms, raising the possibility of attrition bias. More patients were lost to follow-up in the supportive care alone arm, perhaps because they did not receive 'active' treatment, but we cannot say whether they were likely to fare better or worse than those remaining in the study. However, the difference in follow-up rates was relatively small (only 3% at the 12-week follow-up point, at which the primary outcome was determined) and we took steps to take account of these issues, by inclusion of recruitment centre and predictors of missing data in the adjusted analyses of outcome. The validity of this approach assumes that the predictors have been correctly identified; if the data were not missing at random (NMAR) then there is still a possibility of bias in the estimates.

Generalisability

The design of the study was very close to real-life practice in terms of the decision GPs face, i.e. whether or not to treat patients with new episodes of depression with SSRI antidepressants, as well as providing support by means of follow-up consultations. It was also close to real-life practice in that the GPs themselves delivered the treatment, so the results are readily generalisable to UK primary care. The pattern of treatment recorded in the GP records in this trial is comparable to that found in routine practice, judging from previous studies of medical record data in UK general practice.[85–87] It is possible to estimate treatment effects, including allowance for both non-compliance with treatment and loss to follow-up, using a complier average causal effect (CACE) analysis,[88] which we will explore and may present in a subsequent publication.

The tallies of surgery logs completed by a number of the study GPs at various points during the study showed that only around 1 in 10 patients with a new episode of depression were referred into the study, mainly because the rest did not fulfil the inclusion criteria, particularly in terms of a lack of equipoise about the benefits of drug treatment on the part of the doctor or patient or both. This raises the question of how representative were the participating patients of all patients presenting with depression, but inevitably we could include in a randomised trial only those patients who were in equipoise about treatment, and whose doctors were in equipoise. It is more difficult to carry out a randomised trial of treatment that is already established in practice, as most doctors and many patients already have opinions about its effectiveness, which would not be such a problem for a trial of a new treatment. We found

evidence that male patients were less likely to be referred into the study, but referred patients were representative in terms of age. We also had relatively few patients referred in the upper age group even though we had issued no age restriction to the GPs. This may reflect known lower rates of treatment in older people (which Age Concern has highlighted in a recent report[89]) or possibly a reluctance to enter older people into a trial, because of the extra demands for assessments which are then placed on them. Qualitative interviews with the participating GPs might have given better insight into why some eligible patients were not referred than did the limited information written in the surgery logs.

Only one in three referred patients was randomised, due partly to a number having HDRS scores outside the required range of severity, but also again due in part to a lack of patient equipoise about the effects of treatment and a subsequent unwillingness to be randomised, especially to the drug treatment arm. However, those patients who were randomised were generally representative in terms of both gender and age of the patients referred into the study. No preference arms were included in the study design, which it might be supposed would have allowed more patients to join the study given that many declined to be randomised owing to a strong preference against having antidepressants. However, piloting of preference arms partway through the study suggested that adding them tended to reduce the numbers of patients agreeing to be randomised, compromising the most important objective of the trial. Again, qualitative interviews might have engendered greater understanding of why so many patients declined to be randomised after accepting referral into the study than did the relatively brief questions asked when consent was withheld.

The inclusion criteria were kept as wide as possible given the constraints of the trial. In addition to the 87 who were excluded because of an HDRS score outside the defined range, a further 50 patients were excluded because they had received antidepressant treatment within the last 12 months. This exclusion criterion was designed to limit the sample to patients presenting with new bouts of depression; it was set at 12 months because depression is a relapsing condition and recurrence of symptoms within 12 months is common, and probably represents a relapse rather than a new episode. We wanted to determine the effectiveness and cost-effectiveness in new episodes and to be clear that we were not dealing with relapsing chronic depression. It is possible that we may have excluded fewer patients if we had relaxed this criterion, but we thought it was important. We do not have any data on the number who would have been excluded if the criterion had been 6 months instead of 12, for example, so we are unable to say whether this criterion was unnecessarily strict.

However, unlike some antidepressant studies, we did not exclude people on the basis of physical comorbidities, and the sample included many patients with physical health problems, evidenced by the number of medications and outpatient attendances for non-mental health problems. This is to be expected in a relatively non-selected primary care sample where one of the inclusion criteria is the presence of somatic symptoms. The patients were found to be similar, in terms of their levels of use of services and generic health status on the SF-36, to those in previous primary care trials of depression treatment.[90–92] We also measured the number of physical symptoms and alcohol consumption so that we could explore the effects on outcome of depression and response to treatment of these very common complicating factors.

Interpretation of the study findings in light of previous research

Changes in primary and secondary outcomes

The results are consistent with our initial hypothesis that treatment with an SSRI plus supportive care is more effective and cost-effective than supportive care alone, for mild to moderate depression in UK primary care. It is also consistent with two out of three of the placebo-controlled studies of antidepressant treatment referred to in Chapter 1, which demonstrated benefits in mild to moderate depression.[25,28,31] The mean differences found in HDRS scores (2.3 at 12 weeks and 1.7 at 26 weeks) are greater than the mean difference of 1.0 found by Judd *et al*.[28] in a placebo-controlled trial of fluoxetine, but not as great as the 2.9 point mean difference found by Perahia *et al*.[31] in their post hoc analysis of two placebo-controlled trials of duloxetine.

A randomised controlled trial of usual care with or without antidepressant medication for primary care patients with depression has recently been carried out in the Netherlands, measuring clinical

effectiveness but not cost-effectiveness.[93] The study was very similar to ours, as patients were randomised to usual care alone (four consultations within 3 months) or to treatment with the SSRI paroxetine plus usual care, although they were followed up for 52 weeks rather than for 26 weeks as in our study. However, the results showed no significant differences between the treatment groups in an intention-to-treat analysis, in terms of depressive symptoms measured using the Montgomery–Åsberg Depression Rating Scale (MADRS),[94] or in terms of mental or physical functioning on the SF-36, although there was slightly greater patient satisfaction in the paroxetine arm at 13 weeks' follow-up (but not at 52 weeks).[93] Post hoc subgroup analysis suggested that patients with more severe depression, but not those with minor depression, might benefit from antidepressant treatment. However, with a sample size of 181, which had fallen to 160 at 13 weeks' follow-up, the trial was smaller than ours and probably lacked sufficient power to detect a clinically significant effect of treatment. It was described as an equivalence trial, but the difference chosen for the power calculation was relatively large, i.e. five points on the MADRS. In fact, the study demonstrated a three-point mean difference in MADRS scores at 26 weeks in favour of the paroxetine arm, which is a similar effect size to ours, but this was not statistically significant in the Netherlands trial. Their patients had to have symptoms for only 2 weeks rather than the 8 weeks specified in our study, so more patients may have had transient depression and recovered without drug treatment. Their patient sample had much greater variance in depression scores at baseline than ours, because they did not specify a narrow range for inclusion as we did, which further reduced the power of the study to detect small differences between arms. The other difference was that a significant minority of patients in their trial received specialised help from mental health services, and this happened twice as often in the usual care arm than in the paroxetine arm. All these factors would tend to reduce the differences found between the two arms in the Netherlands trial.

As we found no significant effect of severity subgroup on response, the results do not support our second hypothesis that SSRI treatment plus supportive care is relatively more effective among patients scoring 16–19 on the HDRS in comparison with those scoring 12–15, in contrast to the previous placebo-controlled study of amitriptyline by Paykel *et al.*,[20] although as stated above the power was limited to detect differences between severity subgroups.

This was not a placebo-controlled trial and the benefits found could be due largely to a placebo effect of the SSRIs. A recent systematic review and meta-analysis by Kirsch *et al.*,[95] of 35 published and unpublished placebo-controlled trials of SSRIs registered with the US Food and Drugs Administration, suggested that there is a significant placebo response to antidepressants which may account for most of their effect in depression except at the highest levels of severity (HDRS scores of 28 or more). It should be noted that the meta-analysis included only one trial in mild depression and its conclusions rested on extrapolation from trials in moderate to severe depression,[95] but it is consistent with previous research suggesting that drug–placebo differences are greater for more severe depression.[96,97]

Drug treatment may be an important symbolic gesture on behalf of the GP in the patient's eyes, conveying the message that the doctor takes the patient's problems seriously and believes it when the patient says that their depression is serious.[98] Antidepressants may help to 'exculpate' patients, invoking a disease, or a biochemical imbalance, as a cause of their problems which allows them to accept less responsibility for the situation in which they find themselves.[99,100] Antidepressants may also help patients to cope better with their problems by improving their sleep and reducing anxiety symptoms, and so help their symptoms of depression indirectly.[11] In relation to this point, however, preliminary analysis of the HDRS results in this study shows that the core symptoms of depression did change, suggesting that sleep and relief of anxiety symptoms were not responsible for the benefits found. A more extensive analysis of the individual HDRS symptoms is planned, and may appear in a subsequent publication.

However, whether or not the benefit of antidepressant treatment found in this study is due to a placebo effect, it is important to consider whether it is a clinically significant effect. Kirsch *et al.*[95] suggest that a difference between arms of less than 3 points on the HDRS is not clinically significant, because this was the drug–placebo difference regarded as significant by the NICE Depression guideline development group.[11] However, we understand that this was a decision based on a consensus arrived at through discussion by clinicians, service users and carers involved in the guideline development, and was not based on

an objective validation of changes in HDRS scores against levels of patient functioning or quality of life. It is also important to note that the mean difference in scores among a group of patients is only the average of a range of individual responses, with some patients improving considerably more than the average and some not improving at all, or even getting worse on treatment, as we showed was the case in this study by means of the box plots of HDRS scores at the three measurement points. It is also important to consider that the HDRS is an ordinal scale, but not an interval scale, which means that a difference of 2 points at the mild end of the spectrum may be more important than a difference of 2 points at the severe end.[101]

It is important to note that the difference in favour of the SSRI plus supportive care arm was found despite the fact that 20% of patients in the supportive care alone arm also received SSRIs. According to the CSRI data, the mean duration of SSRI treatment taken was 144 days, and two-thirds of participants prescribed SSRIs reported using them for the whole of the 26-week period. Further analysis of the number, dates and length of prescriptions for each patient according to their GP records will be carried out to determine the duration of treatment, which is likely to be more accurate than patient recall over 26 weeks. It is important to note that, although guidelines recommend at least 6 months' treatment with antidepressants,[11] the pattern of prescribing recorded in the GP records is comparable with previous medical record-based studies of the amount and duration of antidepressant treatment in UK general practice.[85–87]

The negative result for the BDI is interesting, given the positive findings for the HDRS. As stated above, this is unlikely to be due to the fact that it is self-completed, since positive changes were seen in the self-completed SF-36 MH and VT subscales and MISS satisfaction scores. It may be because the version of the BDI that we used measures different aspects of depression to the HDRS and is less sensitive to change. There is evidence that the BDI measures more trait-like features of personality such as chronic low self-esteem and pessimism rather than the core symptoms of depression.[102] The HDRS is closer to the DSM-IV concept of depressive disorder[7] because it measures the mandatory symptoms of depression (depressed mood, loss of interest), all the somatic and most of the cognitive symptoms, whereas the BDI primarily measures cognitive symptoms.[103] As a result the BDI shows a lack of sensitivity to change with physical treatments such as antidepressants when compared with the HDRS or the MADRS.[102] The BDI is more likely to improve in trials of psychotherapy such as cognitive behaviour therapy where chronic low self-esteem is usually a specific target of the treatment. The version of the BDI we used in this study has been replaced by a second edition, the BDI-II. One of the main objectives of this new version was to improve its content validity by adding, eliminating or rewording items to conform more closely to the US DSM-IV diagnostic criteria for depression. As a result, the BDI-II displays greater reliability and sensitivity to change.[104]

The observed changes in SF-36 scores over the 26 weeks were similar to those found in previous studies of treating depression in primary care in both the UK and the US. The HTA-funded Assessing Health Economics Antidepressants Study (AHEAD) comparison of the health economics of three classes of antidepressants reported changes in mean MH scores over 6 months of treatment from 37 at baseline rising to 70, comparable to the change from 39 to 61 in the SSRI plus supportive care group in this study.[92,105] In the AHEAD study, the role – emotional (RE) scores rose from 23 to 58 and the general health (GH) scores rose from 54 to 65, which again were comparable to the changes we saw in the SSRI-treated group from 18 to 58 for RE and from 49 to 61 for GH.[92,105] Lin *et al*.,[91] in their trial of collaborative stepped care for depression, reported changes over 6 months in mean social functioning (SF) scores, rising from 50 at baseline to 71 in treated patients and from 52 rising to 68 in controls, comparable to the changes we found in SF scores (46 rising to 71 and 44 rising to 68 respectively). They found changes in RE scores from 26 rising to 55 in treated patients and from 24 to 52 in controls, again comparable to the changes we found in RE scores (17 rising to 59 and 19 rising to 57 respectively).[91]

Differences between arms in the mean total scores on the MISS, although statistically significant, were relatively small, with a difference of only 5 points between 150 in the supportive care alone arm and 155 in the SSRI plus supportive care alone arm. We plan to carry out a factor analysis of the MISS scores, to determine which of the underlying factors within the questionnaire changed and which did not change, and this may appear in a subsequent publication.

Predictors of outcome

It is striking that the negative effect of unemployment at baseline on HDRS and SF-36 scores at follow-up was as large as the positive effect of adding an SSRI to supportive care, which is consistent with previous research showing the important relationship between unemployment and depression.[35,37] Frank *et al*.,[106] in their trial of treating minor depression, found that remission was more likely among patients who were in employment.

Life events and difficulties have been found repeatedly to be related to the onset of depression[40–42,107,108] and to recovery,[44,109–111] but in this study neither provoking agents in the previous year nor ongoing severe interpersonal difficulties at baseline were significant predictors of outcome. Further exploration of life events and difficulties both before entry and during the course of the trial is ongoing. Initial exploration does suggest that the presence of a severe interpersonal difficulty at baseline may reduce the likelihood of remission to HDRS < 8 in the absence of a positive life event post baseline, so a positive life event during the course of treatment may act as a moderator, to increase the likelihood of remission. This requires further analysis and may appear in a subsequent publication. Further analysis is also planned of the nature of the supportive care patients reported that they received in the GP consultations through the PSAC questionnaire, and possible relationships between life events and difficulties, supportive care received, depressive symptoms and patient satisfaction.

Other studies of depression in primary care have shown important effects of psychosocial factors, in addition to those listed in Chapter 1. Walker *et al*.[112] found that psychosocial vulnerabilities, including a history of childhood emotional abuse and loneliness, were associated with a poorer response to a collaborative care intervention. More recently, Lyness *et al*.[113] reported that poorer subjective social support conferred a higher risk for poor outcome.

The outcome on the HDRS was worse for those with a greater number of physical symptoms at baseline. Rubinstein *et al*.[114] also found that fewer common physical symptoms at baseline predicted a better outcome at 6 months' follow-up, along with a lower severity of depression symptoms at baseline, the presence of social support and having completed 3 months of antidepressants at sample entry. However, we found no evidence that a greater number of physical symptoms affected patient responses to treatment, which is in line with previous studies suggesting that patients with depression accompanying physical health problems can still benefit from antidepressant drug treatment.[54] It is interesting to note that the number of physical symptoms was not related to outcome on the BDI. This may be because the HDRS includes somatic symptoms of depression and so is likely to correlate with the BSI to an extent, whereas the BDI measures more cognitive aspects of depression.

Predictors of response to treatment

It is important to stress that the lack of significant interactions between the possible predictors and response to treatment means that we have not identified any ways in which GPs might make decisions about which patients to treat with antidepressants. The addition of an SSRI to supportive care improved outcome in terms of the HDRS whether or not the patients had high numbers of somatic symptoms, and whether or not the patient was unemployed, which implies that GPs should not base decisions on whether to treat a patient with an SSRI on the patient's presentation with physical symptoms or their employment status.

Chapter 7
Conclusions

Implications for practice

The results of this study demonstrate that GP prescribing of SSRI antidepressants for patients with mild to moderate depression, on top of supportive care provided over four consultations in 12 weeks, is more effective than supportive care alone, and is cost-effective at the levels used by NICE to make judgements about recommending treatments within the NHS. However, the results do not support a policy of indiscriminate prescribing to all general practice patients with depression, and we should emphasise certain caveats.

First, our inclusion criteria included persistent symptoms of depression for at least 8 weeks. This study has not provided any evidence to support prescribing for patients with a shorter duration of symptoms. Current NICE guidance advises a period of watchful waiting before considering prescription of antidepressants, and our results support a policy of waiting until patients have had symptoms for at least 8 weeks, and then treating them with an SSRI if they have not improved, in line with NICE guidance.

Second, patients had to score at least 12 on the HDRS for inclusion which, while close to the mildest end of the spectrum of depression, does not include all patients diagnosed as depressed by their GPs. We excluded 47 patients out of 602 referred into the study as a result of HDRS scores of less than 12. We chose this threshold as it corresponded to the lower end of the severity range on the HDRS for which benefit has been shown in placebo-controlled trials.[20,25,31] Previous research has shown evidence of functional impairment due to very mild depression,[12,13] right down to a level of 7 on the HDRS,[115] but this study has not provided any evidence to support prescribing for very mild depression below a score of 12. This score on the HDRS is at the threshold level of severity for diagnosing mild major depressive disorder, as discussed in Chapter 1, and corresponds approximately to a score of 12 on the Patient Health Questionnaire, 9-item version (PHQ-9),[116,117] or a score of 9 on the Hospital Anxiety and Depression Scale depression subscale (HADS-D).[116] These two measures are now commonly used to measure the severity of depression in UK practices as a result of the inclusion of incentives to measure severity in the UK GP contract quality and outcomes framework in April 2006. We can therefore recommend, on the basis of these findings, that SSRI antidepressants should be considered in someone who has been experiencing symptoms for at least 8 weeks and has a PHQ-9 score of 12 or more or a HADS-D score of 9 or more.

Given that there may be benefits to be gained from prescribing SSRIs for mild depression, we need to consider whether these benefits outweigh the possible adverse effects in any individual patient. It is important to consider the risk of overdose, as illustrated by two patients who took overdoses of paracetamol during the course of this trial, although fortunately none took an overdose of SSRIs. The side effects of medication are generally minor, as we found in this study, but occasionally can be severe and include, for example, the potentially fatal serotonin syndrome. Patients with epilepsy may suffer fits due to the lowering of the seizure threshold by antidepressant medication, which may stop them driving and cause them to lose their job. In addition to these physical risks of medication, prescribing may be perceived as 'disposing' of the patient, precluding a greater exploration of their life difficulties,[118,119] and of non-drug strategies to tackle depression, although we found no evidence of differences between arms in reported discussion of non-drug strategies in this study. The increasing availability of non-drug treatment alternatives such as computerised CBT-based self-help[15] and psychological therapies[120] may obviate the need to risk prescribing for more and more practitioners in the future.

Implications for further research

More research is needed on the natural history of mild to moderate depression and predictors of chronicity because, although many patients recover within weeks in the absence of treatment, a significant proportion do not remit in the short term (more than 45% at 6 months in this study).

Better ways of early identification of those who are less likely to recover in the short term would help GPs to target additional treatment or referral for psychological or psychiatric treatment to those more likely to need extra help.

More placebo-controlled studies of antidepressants for mild depression in primary care are needed, as the evidence base for the treatment of mild depression in particular is still relatively small.[11,23,84,95] More research is also needed into self-help, exercise, diet and novel non-drug treatments for mild depression, as the evidence base for non-drug treatments is also very small.[11]

More research is required into the differences between the HDRS and BDI and other measures of depression, to explore whether they measure different aspects of depression and whether there are differences between them in sensitivity to change in relation to drug, psychological and other treatments.[103] This would help to inform the choice of the most appropriate measure for future trials. We intend to look at the elements of the HDRS and BDI in this study for a possible future publication.

More research is needed into supportive care or watchful waiting,[11] to explore the therapeutic aspects, what supportive care should include and how to optimise it. We intend to look further into the relationship between reported consultation content, life events and difficulties and outcome in this study, including patient satisfaction. We will also carry out an exploratory factor analysis of underlying constructs in the MISS measure of satisfaction used in this study.

Finally, better measures of outcome for depression studies need to be developed, including patient-derived measures. The Psychological Outcome Profiles (PSYCHLOPS) measure developed at King's College London is one such instrument, which is intended to measure change in those issues of importance to the individual patient or client, and is ideally suited to situations where clients present with varied mental health issues that might not be adequately captured by standardised instruments (see www.psychlops.org.uk).

Conclusion

Treatment with an SSRI plus supportive care is more effective than supportive care alone for patients with mild to moderate depression in UK primary care, at least for those with symptoms persisting for 8 weeks and with an HDRS score of 12 or more. The additional benefit is relatively small, and may be at least in part a placebo effect, but is probably cost-effective at the levels used by NICE to make judgements about recommending treatments within the NHS.

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Contribution of authors

Tony Kendrick (Professor of Primary Care) was the Chief Investigator and was involved in the conception and design of the study, interpretation of data, drafting and revising the report and approving the final version. Judy Chatwin (Trial Co-ordinator) was involved in modifying the design of the study, data collection, analysis, drafting and revising the report and approving the final version. Chris Dowrick (Professor of Primary Medical Care), André Tylee (Professor of Primary Medical Care and Mental Health), Richard Morriss (Professor of Psychiatry and Community Mental Health), Robert Peveler (Professor of Liaison Psychiatry) and Tirril Harris (Visiting Research Fellow) were involved in the conception and design of the study, interpretation of data, drafting and revising the report and approving the final version. Morven Leese (Reader in Medical Statistics) and Paul McCrone (Reader in Health Economics) were involved in the conception and design of the study, analysis and interpretation of data, drafting and revising the report and approving the final version. Michael Moore (Senior Lecturer), Richard Byng (Senior Clinical Research Fellow), George Brown (Professor Emeritus), Mark Gabbay (Head of Division of Primary Care) and Tom Craig (Professor of Social and Community Psychiatry) were involved in modification of the design, interpretation of data, drafting and revising the report and approving the final version. Sophie Barthel (Research Associate) was involved in analysis and interpretation of data, drafting and revising the report and approving the final version. Helen Mander (Researcher), Adele Ring (Researcher), Vikki Kelly (Researcher) and Vuokko Wallace (Researcher) were involved in modification of the design, data collection, revising the report and approving the final version. Anthony Mann (Professor Emeritus) was involved in the conception and design of the study, revising the final report and approving the final version.

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Chatwin J, Kendrick TR. Protocol for the THREAD (THREshold for AntiDepressants) study: a randomised controlled trial to determine the clinical and cost effectiveness of antidepressants plus supportive care, versus supportive care alone, for mild to moderate depression in UK general practice. *BMC Fam Pract* 2007;**8**(1):2.

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Appendix 1
Initial letter to GPs

Version 3 5/7/04

Dear Dr

Trial of SSRIs for mild to moderate depression in primary care

We would like your help with an important study of treatment for depression. This project has been funded by the NHS R&D Health Technology Assessment programme and we are aiming to recruit patients from general practices around three centres: Southampton, London (co-ordinated by the Institute of Psychiatry and King's College London) and Liverpool.

What is the research question?

Current clinical guidelines recommend antidepressant medication as first-line treatment for depression in primary care, at least if patients fulfil criteria for major depressive disorder. However, as you know, antidepressants are often prescribed for depressive symptoms below the threshold for major depression. There has been relatively little research in primary care to guide us on the severity threshold at which antidepressants should be offered. Another issue that needs to be addressed is whether predictors of response to antidepressant treatment can be identified, to help us decide which patients should be offered them.

To address these questions we will carry out a randomised controlled trial of SSRIs versus supportive care alone, measuring possible predictors of response at baseline.

What would you have to do?

We would ask you to refer to the study patients that you find to be depressed in your surgery consultations, for whom the decision whether or not to prescribe an antidepressant is uncertain (please see the enclosed sheet giving inclusion and exclusion criteria). To avoid asking too much of you in busy appointment slots, we would like you simply to outline the nature of the study, hand out an information sheet describing the trial and ask whether the patient is willing to see a researcher to discuss possible enrolment. Patients referred to the researcher (by fax, at your convenience) will be contacted within a few days, given more information in person about the study, and asked for their consent in writing (please see the enclosed patient information sheet).

Patients included in the study would need a follow-up consultation arranged with you two weeks after the initial consultation, to begin treatment if appropriate, then further follow-ups two, four, eight, and twelve weeks after the second consultation. You would be asked to prescribe an SSRI for those randomised to the active treatment arm, and to give supportive care to those in the non-drug arm, in follow-up 10-minute surgery appointments. Patients in both arms may be referred for counselling if you wish. If patients in the non-drug arm become clinically worse, you will be free to prescribe antidepressant drugs if this is indicated, in your judgement. Patients in the SSRI arm should be treated for four months after recovery.

How much work is involved?

We hope that you might recruit between two and four patients for the study, over a 6 month period, although the study will actually be accepting patients for 15 months and should you wish to continue, your involvement would be much appreciated. Your practice would be paid NHS R&D service support costs for the extra consultations involved. This would be at locum rates as advertised in *Medeconomics*. There would also be payment for your staff time spent retrieving the patients' medical records for the researchers, at the end of the study.

What do you need to do next?

Please would you think about possible involvement in this study, and discuss it with your partners. They do not have to be involved too, if you do agree to take part yourself. We will telephone your Practice Manager in two weeks to see whether you might be interested. If you are interested, we would like to come and describe the study to you in more detail, and answer any questions you may have.

We hope that you will consider joining us in this important study which should establish the threshold of severity for the prescription of antidepressants in general practice, including identifying possible predictors of patient response. Such information is vital for our day to day practice.

We look forward to discussing this further with you.

Best wishes.

Yours sincerely

Tony Kendrick

Appendix 2

Summary sheet for GPs

Version 3
Dated 5/7/04

STUDY OF SSRIs PLUS SUPPORTIVE CARE vs SUPPORTIVE CARE ALONE FOR MILD TO MODERATE DEPRESSION IN PRIMARY CARE
(THREshold for AntiDepressants STUDY)

The purpose of the study is to consider whether treatment with an SSRI plus supportive care is more effective and cost-effective than supportive care alone. If it is more effective, does this apply across the whole range of severity of symptoms of mild depression? The study will also consider what patient factors might predict a beneficial response.

Inclusion criteria

Patients attending surgery who:
- are found to be depressed and potentially in need of antidepressant treatment
- have had symptoms of depression for at least four weeks
- are aged 18 years and above
- have somatic as well as psychological symptoms.

Exclusion criteria

The following patients are not suitable for inclusion:
- Those with depression that definitely requires treatment with antidepressants
- Those already in contact with psychiatric services
- Those already receiving cognitive–behavioural treatment or counselling
- Those for whom substance misuse requires specific treatment
- Those with any active suicidal intentions
- Pregnant or breast-feeding women, or women of child-bearing age without satisfactory contraception
- Those considered to be too physically unwell to participate
- House-bound patients
- Those without the spoken and written language skills necessary to take part
- Temporary residents
- Patients where SSRIs are contraindicated
- Those who have received treatment for depression within the previous 12 months
- Those who continue to take St John's Wort.

Recruitment procedure

The GP should simply outline the nature of the study, hand out the information sheet describing the trial, and determine whether the patient is willing to see a researcher to discuss possible randomisation.

Patients who indicate that they are willing to discuss participation in the trial should be referred by the GP, by fax, to the researcher at the local centre, giving the patient's name and contact details. Patients referred to the study will be contacted by a researcher at each site, as soon as possible after referral, usually within two days but always within the week, to arrange an initial face to face contact, either at the patient's home or at the doctor's surgery, if the patient prefers. The researcher will explain the study procedures in detail to the patient, give written information, and then visit one week later to ask for their informed consent in writing to participate.

Patient involvement

Patients will be interviewed and will complete questionnaires, including questions about their sociodemographic details, depressive symptoms, social functioning, life events, depressive thoughts, physical symptoms, social support and quality of life.

What happens after the assessment interview?

If the patient is suitable for inclusion in the study then:

- the patient is randomised
- a copy of the consent form and allocated treatment arm are faxed through to the practice
- the GP needs to see the patient about 2 weeks after referral to the study.

If the patient is unsuitable for inclusion in the study, a fax will be sent to the practice informing them of the reasons why the patient could not be randomised and if they will be reassessed at a later date or not.

If the patient is undecided about participation but is willing to be contacted at a later date, a fax will be sent saying that the patient is agreeable to being contacted again in 4 weeks.

GP INVOLVEMENT

Patients in both arms will need to be seen for review of symptoms at follow-up appointments 2, 4, 8 and 12 weeks after randomisation. Those in the supportive care-alone arm should not usually be prescribed antidepressants, since the aim of the study is to determine whether this practice is necessary in milder depression, but this may be over-ridden if the patient's depression worsens and in the GP's clinical judgement the patient needs drug treatment.

Guidelines

If the patient has been randomised to **SSRIs** then the following guidelines are suggested:

Initial consultation following randomisation	**2 week follow-up**	**4 week follow-up**	**8 week follow-up**
Discuss the outcome of the randomisation with the patient, choose and prescribe an appropriate SSRI and carry out the consultation in your usual way	Address any side effects and re-emphasise that treatment often takes a few weeks to work and should not be discontinued without discussion	If the patient has not responded then consider increasing the dose, assuming no intolerable side effects	If the treatment is still unsuccessful then it is suggested that the patient be changed to an alternative drug

If the treatment is successful, it is suggested that treatment is continued for 4 months after recovery.

Local Researcher:
Helen Mander (Southampton) Phone
Vuokko Wallace (London) Phone
Adele Ring (Liverpool) Phone

Study Co-ordinator: Judy Chatwin
Phone or fax:
Mobile phone:
E-mail:

<Study web address>

Appendix 3

Consent to be contacted by researcher

Referral no. (for office use)

Study of SSRI antidepressants for mild to moderate depression

Version 2 dated 5/7/04

There is no obligation to take part, and by signing this form you only agree to allow your doctor to give your contact details to the research team.

Please note that you have the right to refuse to participate in the study or to withdraw at any stage after you have agreed to take part; this will not affect the care you receive from your doctor, who will continue to care for you as normal.

Patient's name	DOB:
Address	Postcode:
Phone number	Best time to contact patient

Patient's signature……..

GP's signature …….. Date ……

Print name …….

Practice name……

I have arranged to see this patient again on ……. *(date)*
(Suggest between 10 days and 2 weeks from today's date for review)

What was the initial presenting complaint?

Please fax this form to the research team on

(023) 00000000

For use by the research team:

Referral no. (for office use)	Date randomised	Date received

Appendix 4

Participant information sheet

Version 5: 5/7/04

Study of antidepressants for mild to moderate depression

You are being invited to take part in a research study. 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 or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

We know antidepressants work for people with more severe forms of depression. They are also being prescribed more in recent years for milder forms of depression, but we don't know if they are necessary in these milder cases. It may be that people with mild depression get better just as quickly with support from their GP and/or counselling from a practice counsellor. It is important for us to know whether the many patients seen by GPs with mild to moderate depression should be offered antidepressants. This three year study aims to find the answer to this question, to guide GPs in their practice in future.

Why have you been chosen?

The symptoms you have described to your GP, such as low mood, tiredness, negative thoughts and sleep difficulties are features of what doctors call mild to moderate depression. We recognise that often they can also be seen as an understandable response to life's difficulties. Your GP would like you to discuss possibly taking part in this study with a member of the research team, who will contact you within the next week. Altogether 300 people will join the study.

What is *mild to moderate depression*?

Most people have changes in mood throughout each day. Most people also have days or even weeks when their mood is lower than usual. Such disturbances of mood are usually mild and pass with time. Occasionally low mood may last longer and, if you seek help, your GP might consider a diagnosis of mild depression. We recognise that some people may feel 'down' or 'stressed' but might not consider themselves to be depressed. Depression is defined clinically by the number of symptoms (see below) that are present; they have to be there for at least two weeks. Moderate and severe depression is distinguished from mild depression because the symptoms are worse and have more of an effect on everyday life. Your GP thinks that the symptoms you are experiencing are in the mild end of the spectrum and are different from severe depression. This spectrum is represented in the diagram below.

What are the symptoms of mild to moderate depression?

Depression affects people in different ways but is generally characterised by a persistently low mood or lack of enjoyment. Other symptoms sufferers often describe include:

- Tiredness and lack of energy
- Poor sleep
- Changes in appetite
- Irritability
- Poor concentration
- Loss of interest and motivation
- Thinking too much about negative things or needless worry
- Physical symptoms such as back or neck pain, churning stomach or palpitations

Do you have to take part?

It is up to you to decide whether or not to take part. A member of the research team will discuss this with you, taking as long as you need, within the next week. If you do decide to take part you will be asked to sign a consent form. You will still be free to withdraw at any time and without giving a reason. If you decide not to take part, or to withdraw at any time, this will not affect the care you receive from your GP or other health professionals involved in your care.

What will happen to you if you take part?

First of all, you will be interviewed by the researcher, either at your doctor's practice, or at your home, or at another convenient place, at a time convenient to you. This interview will take approximately 1½ hours, and if necessary can be completed over two visits. The interview will include questions about your age, occupation, marital status, home background, education, past history, current symptoms, quality of life, and recent life events which might have led to depression. We would like to audiotape part of the interview, with your permission, to make sure we have sufficient detail about the context and meaning to you of any recent life events which might have contributed to depression.

Following this initial interview, a researcher from the study will contact you to tell you whether or not you are being asked to take the antidepressant, you will also be asked to return to see your GP. Whether you are in the group to be prescribed an antidepressant, or in the group to be followed up with supportive care alone, will be determined by a computer which has no information about you – that is, by chance. You have a one in two chance of being prescribed antidepressant medication.

What do you have to do?

If you are put into the group to be given an antidepressant, we would like you to take this medication regularly, each day, (it often takes two to three weeks to start working). Whichever of the two groups you are in, we would also like you to see your GP for further check-ups after 2, 4, 8, and 12 weeks.

Twelve weeks after the start of your involvement in the study you will be interviewed again by the researcher, who will ask you about your symptoms, how these have affected your life, and the treatments you have received. This interview should take around 1 hour. A further research interview, with similar questions, lasting around an hour and a half, will then take place six months after the start of the study. Your involvement would then be finished. At the end of six months, sections of your general practice medical records would be looked at by the researcher to check what treatment you have received.

What is the medicine being tested?

A type of antidepressant known as a selective serotonin reuptake inhibitor, or SSRI. These are antidepressant drugs which are licensed for use in depression and have been in regular use in the UK

for several years – they are *not* experimental treatments. We know they are generally very safe drugs which usually cause few side-effects. Recognised side-effects include nausea, stomach ache, diarrhoea or constipation, changes in appetite, and changes in the pattern of sleep. Less common side effects include nervousness, headache, tremor, dizziness, drowsiness, rashes, joint pains, and sexual difficulties. Rare side effects include retention of urine, visual disturbances, changes in blood sugar, fever, abnormal bleeding, hair loss, and possibly aggressive behaviour.

If you are put in the group asked to take an antidepressant, and you suffer any symptoms you think might be side-effects, please mention these to your GP at the follow-up appointments, or sooner if you are concerned, by contacting your GP's practice. If you suffer mild side-effects, such as an upset stomach, we would like you to continue taking the medicine if you are able. If you are in doubt, stop taking it and discuss it with your GP at the next follow-up appointment.

What are the possible disadvantages and risks of taking part?

If you are put into the antidepressant treatment group, the main risk is that of developing side-effects, as above. However your GP will be asking you about these effects during the follow-up, and if necessary will stop giving you the medication, to stop you suffering the side-effects.

What are the possible benefits of taking part?

If you are put into the antidepressant group, it is possible that you may recover from your depression more quickly. However, we do not know if this is the case – the study is designed to find this out. We hope that the supportive care you receive from your GP and/or counsellor, whichever group you are put into, will help you get better quickly in any case.

The information we get from this study may help us to treat future patients with mild to moderate depression better.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your GP will tell you about it and discuss whether you want to continue in the study. If you decide to withdraw your GP will arrange for your care to be continued in the usual way. If you decide to continue in the study you will be asked to sign an updated consent form.

Confidentiality

All information which is collected about you during the course of the research will be kept strictly confidential; the only exception would be if the interview revealed a significant risk of harm to yourself or others, in which case information may be fed back to your doctor but only after discussion with you. Any information about you which leaves the practice will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the study?

The results should be published in a medical journal within 18 months of the end of the study. They will also be fed back to your GP. You can obtain a copy of the results from the research team, through your GP. You will not be identified in any report or publication arising from the study.

Who is organising and funding the study?

The study has been funded by the Department of Health, through the National Coordinating Centre for Health Technology Assessment. It has been organised by the Universities of Southampton, London and Liverpool. Your doctor is not being paid anything extra for including you in this study, beyond the usual costs of the consultations arranged for your follow-up.

Who has reviewed the study?

The study has been reviewed and approved by the Local Research Ethics Committee.

Contact for further information

Study Co-ordinator		Phone
Local Researcher	(Southampton)	Phone
Local Researcher	(London)	Phone
Local Researcher	(Liverpool)	Phone

Appendix 5

Consent form to participate

Version 3, 5/7/04

Centre Number: 1

Study Number: APM/MREC/02/7/091

Patient Identification Number for this trial:

CONSENT TO PARTICIPATE IN STUDY

Title of Project: Study of SSRI antidepressants for mild to moderate depression

Name of Researcher:

	Please initial box
1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study and have had the opportunity to ask questions.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that my interview with the researcher will be audio tape-recorded.	
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Southampton or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
5. 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

Appendix 6

Consent form if undecided

Version 2: 5 July 2004

Centre Number:

Study Number: APM/MREC/02/7/091

Patient Identification Number for this trial:

CONSENT TO BE RECONTACTED

Title of Project: Study of SSRI antidepressants for mild to moderate depression

Name of Researcher:

I am unsure about participating in the above study at present but am willing to be contacted again in 4 weeks time to reconsider the possibility of taking part.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from Researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 7

Fax to GP indicating randomisation arm

Randomisation date:

Randomisation ID:

Referral number:

RANDOMISATION

FAX FROM THE THREAD STUDY
CONFIDENTIAL

For the attention of:

Thank you for referring:

DOB:

who was seen by a researcher on …..

The patient's rating on the Hamilton Depression Rating Scale (HDRS) is …… (the mild to moderate range is 12 to 19) and they have been randomised to:

☐ SUPPORTIVE CARE WITH AN SSRI

Please can you ensure that the above patient receives an appropriate prescription for an SSRI. They have been informed of their need to collect a prescription from the surgery but have been advised to telephone the practice prior to collection. Please can you arrange to see the above patient for supportive care, as close as possible to the dates below. Thank you.

☐ SUPPORTIVE CARE ALONE

Please can you ensure that you see the above patient for supportive care as close as possible to the following dates. Thank you.

Suggested dates for follow-up supportive care

2 weeks after randomisation

4 weeks after randomisation

8 weeks after randomisation

12 weeks after randomisation

The patient has already made an appointment with you for … to discuss the outcome of the randomization, this is in addition to the suggested dates above. Thank you very much for your support with this study and we look forward to hearing from you again soon. If you have any questions please contact the Study Co-ordinator (……)

Tel and Fax:
Mobile:
Email:

Appendix 8

Fax to GP – patient not suitable for study

Randomisation no:

Randomisation date:

EXCLUSION

FAX FROM THREAD STUDY
C O N F I D E N T I A L

For the attention of:

Thank you for referring:

DOB:

who was seen by a researcher on …..

☐ After further discussion, they declined to take part

This patient's rating on the Hamilton Depression Rating Scale (HDRS) is ……., the mild to moderate range is 12 to 19, for patients in this study.

The patient completed the PHQ-9 on ..... and their score was PHQ-9
The patient completed the HADS-D on ..... and their score was ..... HADS-D
The patient completed the BDI on ..... and their score was ..... BDI

They will not be continuing in the trial because:

☐ their rating on the HDRS is too high for this study (current guidelines suggest that patients with depressive symptoms of this severity should be offered treatment, which may include antidepressants)

☐ their rating on the HDRS is too low

☐ their symptoms have not been present long enough and they do not want to wait before receiving treatment

☐ other …….

We have asked the patient to come back and see you to discuss their further management.

Thank you for taking the time to refer the above patient and please do continue to refer patients into the study. We look forward to hearing from you again very soon. The patient has been made aware that they will not be continuing with the trial.

In the meantime if you have any questions please contact:

Study Co-ordinator:
Phone or fax:
Mobile phone:
E-mail:

Local Researcher:
Phone:
Fax:
E-mail:

Appendix 9

Hamilton Depression Rating Scale (HDRS): 17-item interview

Referral No. Randomisation ID.

STRUCTURED INTERVIEW FOR HAMILTON DEPRESSION RATING SCALE

The interview is semi-structured with certain standard questions that should be asked in a standardised way. If circumstances necessitate some modifications, then please feel free to make them. When an answer is affirmative, you should always follow up the answer with further questions of your own to amplify the answer, and clarify the nature, frequency and severity of the symptom. A few of the listed questions need not be asked if evidence indicates that they are not relevant. In general the order of items permits comfortable clinical interviewing. In case of very severe illness or if other circumstances require departure from the standardised order, this is permissible.

Ratings

For most items, the time period to be rated is the last week, averaging where symptom levels have fluctuated. The condition is to be rated retrospectively over the last week on the basis of the history supplied by the patient. The rating is an average of typical symptoms over the time, taking into account frequency if the symptoms are episodic. In a few items, such as suicide, which are indicated in the text, maximal rather than average behaviour is rated.

For the remaining items, indicated specifically in the schedule, the rating is of observable behaviour or verbal interaction at interview.

When the scale has been completed, transfer the scores onto this sheet and total them.

	Score		Score
HAM 1		**HAM 10**	
HAM 2		**HAM 11**	
HAM 3		**HAM 12**	
HAM 4		**HAM 13**	
HAM 5		**HAM 14**	
HAM 6		**HAM 15**	
HAM 7		**HAM 16**	
HAM 8		**HAM 17**	
HAM 9		**TOTAL**	

Referral No: Randomisation ID No:

Date: Timepoint:

Date completed

Referral No. Randomisation ID.

'I am going to ask you some questions about how you have been feeling over *the last week*.'

Depressed Mood

Rate the average severity of the subjective feelings of depressed affect, as judged by verbal complaints of depression, sadness, gloom, dejection, etc. Do not include such aspects as pessimism, worthlessness, suicide, depressed appearance, which are to be rated separately. Where feelings fluctuate, take into account frequency.

'*Over the last week* have you felt depressed? How would you describe it? How often does it come and go? How long does it last? Moody? Down hearted? Dejected? Sad? Blue? Does crying relieve it? Do you feel beyond tears? How bad is it? So bad that it is excruciating or very painful?'

HAM 1 ☐

0 = Absent.
1 = Gloomy attitude, pessimism, hopelessness only on questioning.
2 = Occasional weeping, depressed mood reported spontaneously verbally.
3 = Frequent weeping, depressed mood communicated non-verbally/look sad (no eye contact etc.)
4 = Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

Anxiety Psychic Symptoms

Demonstrated by tension, difficulty in relaxing, irritability, worry over trivial matters, apprehension and feelings of panic, fears, difficulty in concentration and forgetfulness, feeling 'jumpy'.

'*Over the past week* have you been feeling nervous, anxious, frightened, scared, or panicky? Have you worried about things, you didn't even need to worry about? Have you found it hard to relax? Have you had a feeling of dread as though something terrible were about to happen?'

HAM 2 ☐

0 = No difficulty.
1 = Subjective tension and irritability.
2 = Worrying about minor matters.
3 = Apprehensive attitude in face or speech.
4 = Fears expressed without questioning.

Date completed

Referral No. Randomisation ID.

Somatic Anxiety

This encompasses a number of somatic complaints common in anxious patients, and presumed to represent autonomic concomitants of anxiety. Consider frequency, intensity, and number of symptoms.

'In the past week have you suffered from anything such as: trembling, shakiness, excessive sweating, feelings of suffocation or choking, attacks of shortness of breath, dizziness, faintness, headaches, pain at the back of the neck, butterflies, or tightness in the stomach? How often? How badly?'

HAM 3 ☐

0 = Absent.
1 = Mild.
2 = Moderate.
3 = Severe.
4 = Incapacitating.

Weight loss

Assess weight change from start of illness (or from usual weight if onset was at a very exceptional time, e.g. during pregnancy).

'How is your weight now compared with the start of your recent episode?'

HAM 4 ☐

0 = No weight loss.
1 = Slight or doubtful weight loss associated with present illness.
2 = Definite (according to patient) weight loss (clothes size decreased).

Somatic Symptoms: Gastro-intestinal

Reported pattern in appetite over last week compared to usual. Where appetite has *fluctuated*, take an average.

'How has your appetite been over the *past week*? How much do you eat?'

HAM 5 ☐

0 = None.
1 = Loss of appetite but eating well without encouragement.
2 = Difficulty in eating without urging. Requests or requires laxatives or medication for GI symptoms.

Date completed

Referral No. Randomisation ID.

Sleep Disturbances

Establish whether the patient is taking sleeping tablets. *Rate the disturbances on the nights he or she is not taking sleeping tablets* if there are any, otherwise rate the disturbance experienced with medication. Ask questions to establish the pattern of sleep on a typical night. Consider the average disturbance during the past week. If problems are variable make allowances for frequency.

'Have you been taking sleeping tablets in the past week? Every night? Have you had any difficulty sleeping or getting off to sleep? When you do get to sleep, do you sleep well, are your restless, or do you keep waking? Do you wake early in the morning? If so do you keep awake or fall asleep again? Have you been able to manage with less sleep than usual without seeming to get tired?'

Insomnia Early – In last week

Difficulty falling asleep. HAM 6 ☐

0 = No difficulty falling asleep.
1 = Complains of occasional difficulty falling asleep, i.e. more than half an hour (less than 5 nights per week).
2 = Complains of nightly difficulty falling asleep (5 nights or more per week).

Middle Insomnia

Sleep difficulty occurring up to five hours after retiring provided it is preceded and followed by a spell of sleep. If the latter criteria are not met, code as initial or delayed insomnia.

HAM 7 ☐

0 = No difficulty.
1 = Patient complains of being restless and disturbed during the night.
2 = Waking during the night – any getting out of bed rates 2 (except for voiding or checking on something/toilet/babies).

Insomnia Late

Early wakening. Include all difficulty occurring between five and eight hours after retiring, and also final awakening earlier than five hours after retiring, provided in both cases patient has been asleep at some earlier stage – not due to shifts or habitual e.g. retired milkman.

HAM 8 ☐

0 = No difficulty.
1 = Waking in early hours of the morning but goes back to sleep.
2 = Unable to fall asleep again if he/she gets out of bed.

Date completed

Referral No. Randomisation ID.

THE FOLLOWING TWO *ITEMS RELATE ENTIRELY TO THE PATIENT'S STATE AT INTERVIEW*

Retardation

Assess solely on *basis of observation at interview*, not subjective complaint of slowing. Rate slowness and diminution of thought and speech, impaired ability to concentrate, decreased motor activity, lack of facial expression.

HAM 9 ☐

0 = Normal speech and thought.
1 = Slight retardation at interview.
2 = Obvious retardation at interview (you are dragging out answers).
3 = Interview difficult.
4 = Interview impossible.

Agitation

Motor restlessness associated with subjective discomfort or tension. Typical features include moving in chair, biting or pursing of lips, tapping fingers, moving feet, pulling at skin or hair, nail-biting, pulling on handkerchief or clothing, biting pencil open, hand wringing, pacing. It should be differentiated from anxiety. It refers to observable phenomena. *Rate on basis of behaviour throughout the interview.*

HAM 10 ☐

0 = None.
1 = Fidgetiness.
2 = Playing with hands or hair, obvious restlessness – constant.
3 = Moving about, can't sit still.
4 = Hand wringing, nail biting, hair pulling, biting of lips, patient is on the run (only if constant).

Date completed

Referral No. Randomisation ID.

Somatic Symptoms: General (energy and fatigue)

Subjective feelings of fatigue, tiredness, lethargy, lack of energy. Consider average in intensity and frequency.

'*Over the past week* have you felt tired easily? All the time? Had you much energy? Was it an effort to do anything? Did you spend a lot of time resting? In bed?'

HAM 11 ☐

0 = None.
1 = Heaviness in limbs, back or head, headaches, muscle aches, loss of energy, fatigability.
2 = Any clear-cut symptoms.

Guilt and Self-depreciation

This refers to patient's verbal expressions which indicate the extent to which his evaluation of himself and his self-esteem are abnormally lowered, and the degree to which he feels to blame for a variety of acts and omissions. Consider intensity and pervasiveness of both guilt and worthlessness.

'In the *past week* have you had a low opinion of yourself? Have you blamed yourself for things you have done in the past or recently? Have you felt guilty about things? Have you felt you have let your friends and family down? Have you felt you are to blame for your illness? In what way? A lot? A little?'

HAM 12 ☐

0 = Absent.
1 = Self-reproach, feels he/she has let people down.
2 = Ideas of guilt or rumination over past errors or sinful deeds.
3 = Present illness is punishment. Delusions of guilt.
4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

Suicidal Tendencies

This refers to the *maximum* degree of suicidal thought and behaviour experienced *over the last week*.

'Have you felt tired of life? Have you thought you would like not to wake up in the morning, when you go to bed at night? Have you felt that life was not worth living? Have you wished you were dead? Have you had any thoughts of taking your life? Have you gone so far as to make any plans to do so? Have you toyed with a gun in your hand, or taken one or two pills? Have you actually made an attempt on your life?'

0 = Absent
1 = Feels life is not worth living.
2 = Wishes he/she were dead or <u>any thoughts</u> of possible death to self.
3 = Suicidal ideas or half-hearted attempt.
4 = Attempts at suicide (any serious attempt rates 4).

HAM 13 ☐

Date completed

Referral No. Randomisation ID.

Work and Activities

Rate actual performance in last week in work, housework, outside interests, social life, etc., irrespective of feelings of inadequacy, i.e. *this is a scale of general functional capacity*. If not in paid employment outside the home, consider all other areas of activity at home and outside including hobbies and interests. With hospitalised patients, consider overall function in all these areas; (e.g. the patient may have some function in areas of social life in hospital, housework at weekends, but total impairment in work through absence; assign an appropriate rating in the impaired range accordingly).

'Has the capacity to work/activities been affected in last week due to your feelings? What have you actually been doing in work, housework, hobbies and interests and social life?'

HAM 14 ☐

0 = No difficulty.
1 = Thought and feelings of incapacity related to activities, work or hobbies.
2 = Loss of interest in activity; hobbies or work either directly reported by patient, or indirectly seen in listlessness, in decisions and vacillation (feels he/she has to push self to work or activities).
3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies, exclusive of ward chores).
4 = Stopped working because of present illness. In hospital, rate 3 if patient engages in no activities except ward chores, or patient fails to perform ward chores unassisted.

Loss of Libido or Increased Sexual Activity

The assessment is based on a pathological change, i.e. a deterioration obviously related to patient's illness. Inadequate or no information should be rated zero.

'Have you found your sexual interest or activities changed in the past week? In what way?'

HAM 15 ☐

0 = Absent.
1 = Mild loss of libido.
2 = Severe loss of libido.

Date completed

Referral No. Randomisation ID.

THE FOLLOWING ITEMS RELATE ENTIRELY TO THE PATIENT'S STATE AT INTERVIEW

Hypochondriasis

This refers to patient's spontaneous concern at interview with bodily complaints and their part in his/her illness, irrespective of whether or not these appear to have a realistic basis. The hypochondriacal patient is concerned with and keeps coming back to bodily symptoms rather than psychic complaints. It may include somatic anxiety symptoms as well as other bodily symptoms. When dealing with depressive delusions of bodily illness, consider particularly the force and frequency with which they are expressed.

Assess solely on basis of observation at interview.

HAM 15 ☐

0 = Not present.
1 = Self-absorption (bodily).
2 = Preoccupation with physical symptoms and thoughts of organic disease.
3 = Strong conviction of some bodily illness.
4 = Hypochondriacal delusions.

Insight

What do you think is the matter with you?
(Could it be a nervous condition?)
(What do you think is the cause of it?)
[Do you think (specify delusions or hallucinations) were part of the nervous condition?]

HAM 16 ☐

0 = Acknowledges being depressed and ill.
1 = Acknowledges illness but attributes cause to bad food, overwork, virus, need for reasons, etc.
2 = Denies being ill at all.

Date completed

Adapted from Hamilton.[19]

Appendix 10

Beck Depression Inventory (BDI)

Referral No. Randomisation ID.
Timepoint:

Here are 21 groups of statements. Please read each group carefully. Then pick out the one statement in each group which best describes the way you have been feeling in the PAST WEEK, INCLUDING TODAY. Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1.	I do not feel sad	0
	I feel sad	1
	I am sad all the time and I can't snap out of it	2
	I am so sad or unhappy that I can't stand it	3
2.	I am not particularly discouraged about the future	0
	I feel discouraged about the future	1
	I feel I have nothing to look forward to	2
	I feel that the future is hopeless and that things cannot improve	3
3.	I do not feel like a failure	0
	I feel I have failed more than the average person	1
	As I look back on my life, all I can see is a lot of failures	2
	I feel I am a complete failure as a person	3
4.	I get as much satisfaction out of things as I used to	0
	I don't enjoy things the way I used to	1
	I don't get real satisfaction out of anything anymore	2
	I am dissatisfied or bored with everything	3
5.	I don't feel particularly guilty	0
	I feel guilty a good part of the time	1
	I feel quite guilty most of the time	2
	I feel guilty all of the time	3
6.	I don't feel I am being punished	0
	I feel I may be punished	1
	I expect to be punished	2
	I feel I am being punished	3
7.	I don't feel disappointed in myself	0
	I am disappointed in myself	1
	I am disgusted with myself	2
	I hate myself	3
8.	I don't feel I am any worse than anyone else	0
	I am critical of myself for my weaknesses or mistakes	1
	I blame myself all the time for my faults	2
	I blame myself for everything bad that happens	3
9.	I don't have any thoughts of killing myself	0
	I have thoughts of killing myself, but I would not carry them out	1
	I would like to kill myself	2
	I would kill myself if I had the chance	3
10.	I don't cry any more than usual	0
	I cry more now that I used to	1
	I cry all the time now	2
	I used to be able to cry but now I can't cry even though I want to	3

Date completed

Referral No. Randomisation ID.
Timepoint:

11.	I am no more irritated now than I ever am	0
	I get annoyed or irritated more easily	1
	I feel irritated all the time now	2
	I don't get irritated at all by the things that used to irritate me	3
12.	I have not lost interest in other people	0
	I am less interested in other people than I used to be	1
	I have lost most of my interest in other people	2
	I have lost all of my interest in others	3
13.	I make decisions about as well as I ever could	0
	I put off making decisions more than I used to	1
	I have greater difficulty in making decisions than before	2
	I can't make decisions at all any more	3
14.	I don't feel I look any worse than I used to	0
	I am worried that I am looking old or unattractive	1
	I feel there are permanent changes in my appearance that make me look unattractive	2
	I believe that I look ugly	3
15.	I can work about as well as before	0
	It takes extra effort to get started at doing something	1
	I have to push myself very hard to do anything	2
	I can't do any work at all	3
16.	I can sleep as well as I used to	0
	I don't sleep as well as I used to	1
	I wake up 1–2 hours earlier than usual and find it hard to get back to sleep	2
	I wake up several hours earlier than I used to and cannot get back to sleep	3
17.	I don't get more tired than usual	0
	I get tired more easily than I used to	1
	I get tired from doing almost anything	2
	I am too tired to do anything	3
18.	My appetite is no worse than usual	0
	My appetite is not as good as it used to be	1
	My appetite is much worse now	2
	I have no appetite at all anymore	3
19.	I haven't lost much weight, if any, lately	0
	I have lost more than 5 pounds	1
	I have lost more than 10 pounds	2
	I have lost more than 15 pounds	3
	I am purposely trying to lose weight by eating less: ❑ Yes ❑ No	
20.	I am no more worried about my health than usual	0
	I am worried about physical problems such as aches and pains; or upset stomach or constipation	1
	I am very worried about physical problems and it's hard to think of much else	2
	I am so worried about my physical problems that I cannot think about anything else	3
21.	I have not noticed any recent change in my interest in sex	0
	I am less interested in sex than I used to be	1
	I am much less interested in sex now	2
	I have lost interest in sex completely	3

Total score

Date completed

Adapted from Beck *et al*.[61]

Appendix 11

Short Form-36 (SF-36)

Referral No. Timepoint: Randomisation ID.

THE SHORT FORM-36 HEALTH SURVEY QUESTIONNAIRE

The following questions ask for your views about your health, how you feel and how well you have been able to do your usual activities. If you are unsure how to answer any questions please give the best answer you can.

1. In general, would you say your health is:

	(please circle one)
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

	(please circle one)
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

Date completed

Referral No. Timepoint: Randomisation ID.

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(please circle one number on each line)

	ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
3.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4.	Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5.	Lifting or carrying groceries	1	2	3
6.	Climbing several flights of stairs	1	2	3
7.	Climbing one flight of stairs	1	2	3
8.	Bending, kneeling or stooping	1	2	3
9.	Walking more than a mile	1	2	3
10.	Walking half a mile	1	2	3
11.	Walking one hundred yards	1	2	3
12.	Bathing or dressing yourself	1	2	3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(please circle one number on each line)

		YES	NO
13.	Cut down on the amount of time you spent on work or other activities	1	2
14.	Accomplished less than you would like	1	2
15.	Were limited in the kind of work or other activities	1	2
16.	Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

Date completed

Referral No. Timepoint: Randomisation ID.

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(please circle one number on each line)

		YES	NO
17.	Cut down on the amount of time you spent on work or other activities	1	2
18.	Accomplished less than you would like	1	2
19.	Didn't do work or other activities as carefully as usual	1	2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(please circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

21. How much bodily pain have you had during the past 4 weeks?

(please circle one)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

22. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

(please circle one)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

Date completed

Referral No. Timepoint: Randomisation ID.

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks …

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23.	Did you feel full of life?	1	2	3	4	5	6
24.	Have you been a very nervous person?	1	2	3	4	5	6
25.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26.	Have you felt calm and peaceful?	1	2	3	4	5	6
27.	Did you have a lot of energy?	1	2	3	4	5	6
28.	Have you felt downhearted and low?	1	2	3	4	5	6
29.	Did you feel worn out?	1	2	3	4	5	6
30.	Have you been a happy person?	1	2	3	4	5	6
31.	Did you feel tired?	1	2	3	4	5	6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

(please circle one)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

Date completed

Referral No. Timepoint: Randomisation ID.

How TRUE or FALSE is each of the following statements for you?

(please circle one number on each line)

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33.	I seem to get ill more easily than other people	1	2	3	4	5
34.	I am as healthy as anybody I know	1	2	3	4	5
35.	I expect my health to get worse	1	2	3	4	5
36.	My health is excellent	1	2	3	4	5

Date completed

Adapted from Ware and Sherbourne.[63]

Appendix 12

Medical Interview Satisfaction Scale (MISS)

Referral No. Timepoint: Randomisation ID.

Patient Satisfaction Questionnaire

The next 2 pages ask you to remember how you felt immediately after the visit.

Please cross a box to show how much you agree on every line.

	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**
I was satisfied	❑	❑	❑	❑	❑	❑	❑
The doctor gave me a poor explanation of my illness	❑	❑	❑	❑	❑	❑	❑
The doctor told me what my illness is	❑	❑	❑	❑	❑	❑	❑
After talking with the doctor I knew just how serious my illness is	❑	❑	❑	❑	❑	❑	❑
The doctor told me all I wanted to know about my illness	❑	❑	❑	❑	❑	❑	❑
I'm not really certain about how to follow the doctor's advice	❑	❑	❑	❑	❑	❑	❑
After talking with the doctor I had a good idea of how long it will be before I am well again	❑	❑	❑	❑	❑	❑	❑
The doctor seemed interested in me as a person	❑	❑	❑	❑	❑	❑	❑
	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**

Date completed

Referral No. Timepoint: Randomisation ID.

	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**
The doctor seemed warm and friendly to me	❑	❑	❑	❑	❑	❑	❑
I felt that this doctor did not treat me as an equal	❑	❑	❑	❑	❑	❑	❑
The doctor seemed to take my problems seriously	❑	❑	❑	❑	❑	❑	❑
I felt embarrassed while talking to the doctor	❑	❑	❑	❑	❑	❑	❑
I felt free to talk with this doctor about private matters	❑	❑	❑	❑	❑	❑	❑
The doctor gave me a chance to say what was really on my mind	❑	❑	❑	❑	❑	❑	❑
I felt really understood by my doctor	❑	❑	❑	❑	❑	❑	❑
The doctor did not allow me to say everything I wanted about my problems	❑	❑	❑	❑	❑	❑	❑
The doctor did not really understand my reason for coming	❑	❑	❑	❑	❑	❑	❑
This is a doctor I would trust with my life	❑	❑	❑	❑	❑	❑	❑
I would hesitate to recommend this doctor to my friends	❑	❑	❑	❑	❑	❑	❑
The doctor seemed to know what (s)he was doing	❑	❑	❑	❑	❑	❑	❑
	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**

Date completed

Referral No. Timepoint: Randomisation ID.

	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**
After talking with the doctor I feel much better about my problems	❑	❑	❑	❑	❑	❑	❑
The doctor has relieved my worries about my illness	❑	❑	❑	❑	❑	❑	❑
Talking with the doctor has not at all helped my worries about my illness	❑	❑	❑	❑	❑	❑	❑
The doctor has come up with a good plan for helping me	❑	❑	❑	❑	❑	❑	❑
The doctor visit has not at all helped me	❑	❑	❑	❑	❑	❑	❑
The doctor seemed to know just what to do for my problem	❑	❑	❑	❑	❑	❑	❑
I expect that it will be easy for me to follow the doctor's advice	❑	❑	❑	❑	❑	❑	❑
I intend to follow the doctor's instructions	❑	❑	❑	❑	❑	❑	❑
It may be difficult for me to do exactly what the doctor told me to do	❑	❑	❑	❑	❑	❑	❑
I'm not sure the doctor's treatment will be worth the trouble it will take	❑	❑	❑	❑	❑	❑	❑
	Very strongly agree	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Very strongly disagree**

Date completed

Adapted from Wolf *et al.*[64]

Appendix 13

Client Service Receipt Inventory (CSRI): baseline

Version 2 dated 31/3/04

1.	Who do you usually live with?	Husband/wife/steady partner	1
		Spouse/partner *and* children	2
		Children (but no spouse/partner)	3
		Parents	4
		Alone	5
		Other _____	6
2.	Employment status	Paid employment – full-time	1
		Paid employment – part-time	2
		Voluntary work (unpaid)	3
		Sheltered work	4
		Registered as unemployed but available for work	5
		Not working/retired due to illness	6
		Retired	7
		Student	8
		Housewife/husband	9
		Other _____	10

3. Please give details of all periods (including the current one) of employment that you have had during the past 6 months.

Employment 1
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Employment 2
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Employment 3
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Please give details of any way in which your health problem has constrained your career in the last 6 months.

---

4. *In the last 6 months*, have you had any contact with hospital services? *(e.g. inpatient admission, outpatient attendance)*

Yes	1
No	0

If yes:

a. Inpatient care:
Reason for stay 1 _____
No. of days in last 6 months _____
Reason for stay 2 _____
No. of days in last 6 months _____
Reason for stay 3 _____
No. of days in last 6 months _____
Reason for stay 4 _____
No. of days in last 6 months _____
Reason for stay 5 _____
No. of days in last 6 months _____

b. Outpatient care:
Reason for attendance 1 _____
No. of attendances in last 6 months _____
Reason for attendance 2 _____
No. of attendances in last 6 months _____
Reason for attendance 3 _____
No. of attendances in last 6 months _____

c. Day care:
Reason for attendance 1 _____
No. of attendances in last 6 months _____
Reason for attendance 2 _____
No. of attendances in last 6 months _____
Reason for attendance 3 _____
No. of attendances in last 6 months _____

d. A and E: Reason for attendance 1 _____

No. of attendances in last 6 months _____

Reason for attendance 2 _____

No. of attendances in last 6 months _____

Reason for attendance 3 _____

No. of attendances in last 6 months _____

5. Please give details of any of the following services that you have used *in the last 6 months*

Service	*Circle*	*No. of contacts*	*Typical duration*	*Was the contact at home?*	*If private, give cost per hour*
General practitioner (face-to-face)	No Yes				
General practitioner (telephone)	No Yes				
Out of hours contact (GP or deputy)	No Yes				
Out of hours contact (nurse)	No Yes				
Practice nurse (at the GP clinic)	No Yes				
District nurse	No Yes				
Community mental health nurse	No Yes				
Other nurse	No Yes				
Health visitor	No Yes				
Counsellor	No Yes				
Other therapist *Type* _____	No Yes				
'Alternative' medicine or therapy *Specify* _____	No Yes				
Psychologist	No Yes				
Psychiatrist (community or primary care based)	No Yes				
Other community based doctor *Specify* _____	No Yes				
Occupational therapist	No Yes				
Social worker	No Yes				

Service	*Circle*	*No. of contacts*	*Typical duration*	*Was the contact at home?*	*If private, give cost per hour*
Home help/home care worker	No Yes				
Care attendant	No Yes				
Community support worker	No Yes				
Housing worker	No Yes				
Voluntary worker (including priest etc.) *Specify* _____	No Yes				
Day centre/drop-in/social club *Name* _____	No Yes				
Self-help group *Name* _____	No Yes				

6. *In the last 6 months*, have you received help from friends or relatives on any of the following tasks, *as a consequence of your emotional problems*?

Type of help	*Circle*	*Helper's relationship to you (see key below)**	*Average number of hours help per week*
Child care *(Circle 'No' if interviewee has no children)*	No Yes		
Personal care *(e.g. washing, dressing etc.)*	No Yes		
Help in/around the house *(e.g., cooking, cleaning etc.)*	No Yes		
Help outside the home *(e.g., shopping, transport etc.)*	No Yes		
Other _____	No Yes		

* Key: 1 = Mother; 2 = Father; 3 = Brother/Sister; 4 = Other relative; 5 = Friend; 6 = Other (please specify)

7. Please list below use of any medications taken over the *last 6 months*. (If the dose has changed please list separately.)

Name of drug	*Dosage (if known)*	*Dose frequency (e.g. daily)*	*For how long have you taken this drug?*
1.	*mg*		
2.	*mg*		
3.	*mg*		
4.	*mg*		
5.	*mg*		
6.	*mg*		
8.	*mg*		
9.	*mg*		
10.	*mg*		
11.	*mg*		
12.	*mg*		
13.	*mg*		
14.	*mg*		
15.	*mg*		

8. Has your illness brought you into contact with police, or the courts, or a solicitor? If so, please give further details. (Interviewer: record number of contacts, number of nights in police cells, days in prison, etc.)

_____

_____

9. Have you used any other services or incurred any specific costs as a result of your illness? If so, please give further details:

_____

_____

_____

_____

Adapted from Beecham and Knapp.[69]

Appendix 14

Client Service Receipt Inventory (CSRI): 6-month follow-up

Version 1 dated 31/3/04

1.	Who do you usually live with?	Husband/wife/steady partner	1
		Spouse/partner *and* children	2
		Children (but no spouse/partner)	3
		Parents	4
		Alone	5
		Other _____	6
2.	Employment status	Paid employment – full-time	1
		Paid employment – part-time	2
		Voluntary work (unpaid)	3
		Sheltered work	4
		Registered as unemployed but available for work	5
		Not working/retired due to illness	6
		Retired	7
		Student	8
		Housewife/husband	9
		Other _____	10

3. Please give details of all periods (including the current one) of employment that you have had during the past 6 months.

Employment 1
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Employment 2
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Employment 3
Occupation _____
Date started _____ Date finished _____
Reason for end of employment _____

Please give details of any way in which your health problem has constrained your career in the last 6 months.

4. *In the last 6 months*, have you had any contact with hospital services? *(e.g. inpatient admission, outpatient attendance)*

Yes	1
No	0

If yes:

a. Inpatient care:

Reason for stay 1 _____

No. of days in last 6 months _____

No. of days in last 3 months _____

Reason for stay 2 _____

No. of days in last 6 months _____

No. of days in last 3 months _____

Reason for stay 3 _____

No. of days in last 6 months _____

No. of days in last 3 months _____

Reason for stay 4 _____

No. of days in last 6 months _____

No. of days in last 3 months _____

Reason for stay 5 _____

No. of days in last 6 months _____

No. of days in last 3 months _____

b. Outpatient care:

Reason for attendance 1 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 2 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 3 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

c. Day care: Reason for attendance 1 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 2 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 3 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

d. A and E: Reason for attendance 1 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 2 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

Reason for attendance 3 _____

No. of attendances in last 6 months _____

No. of attendances in last 3 months _____

5. Please give details of any of the following services that you have used *in the last 6 and 3 months*

Service	*Circle*	*No. of contacts in last 6 months*	*No. of contacts in last 3 months*	*Typical duration*	*Was contact at home?*	*If private, give cost per hour*
General practitioner (face-to-face)	No Yes					
General practitioner (telephone)	No Yes					
Out of hours contact (GP or deputy)	No Yes					
Out of hours contact (nurse)	No Yes					
Practice nurse (at the GP clinic)	No Yes					
District nurse	No Yes					
Community mental health nurse	No Yes					
Other nurse	No Yes					
Health visitor	No Yes					
Counsellor	No Yes					
Other therapist *Type* _____	No Yes					
'Alternative' medicine or therapy *Specify* _____	No Yes					
Psychologist	No Yes					
Psychiatrist (community or primary care based)	No Yes					
Other community based doctor *Specify* _____	No Yes					
Occupational therapist	No Yes					
Social worker	No Yes					
Home help/home care worker	No Yes					
Care attendant						

Service	*Circle*	*No. of contacts in last 6 months*	*No. of contacts in last 3 months*	*Typical duration*	*Was contact at home?*	*If private, give cost per hour*
Community support worker	No Yes					
Housing worker	No Yes					
Voluntary worker (including priest etc.) *Specify* _____	No Yes					
Day centre/drop-in/social club *Name* _____	No Yes					
Self-help group *Name* _____	No Yes					

6. *In the last 6 and 3 months*, have you received help from friends or relatives on any of the following tasks, *as a consequence of your emotional problems*?

Type of help	*Circle*	*Helper's relationship to you (see key below)**	*Average number of hours help per week in last 6 months*	*Average number of hours help per week in last 3 months*
Child care *(Circle 'No' if interviewee has no children)*	No Yes			
Personal care *(e.g. washing, dressing etc.)*	No Yes			
Help in/around the house *(e.g., cooking, cleaning etc.)*	No Yes			
Help outside the home *(e.g., shopping, transport etc.)*	No Yes			
Other _____	No Yes			

* Key: 1 = Mother; 2 = Father; 3 = Brother/Sister; 4 = Other relative; 5 = Friend; 6 = Other (please specify)

7. Please list below use of any medications taken over the *last 6 months*. (If the dose has changed please list separately.)

Name of drug	*Dosage (if known)*	*Dose frequency (e.g. daily)*	*For how long have you taken this drug?*
1.	*mg*		
2.	*mg*		
3.	*mg*		
4.	*mg*		
5.	*mg*		
6.	*mg*		
8.	*mg*		
9.	*mg*		
10.	*mg*		
11.	*mg*		
12.	*mg*		
13.	*mg*		
14.	*mg*		
15.	*mg*		

8. Has your illness brought you into contact with police, or the courts, or a solicitor? If so, please give further details. (Interviewer: record number of contacts, number of nights in police cells, days in prison, etc.)

_____

_____

9. Have you used any other services or incurred any specific costs as a result of your illness? If so, please give further details:

_____

_____

_____

_____

Adapted from Beecham and Knapp.[69]

Appendix 15

Sociodemographic interview

Version 2 dated 31/3/04

Q1. Gender

☐ 1. Male
2. Female

Q2. Date of birth (dd/mm/yy)

☐☐ ☐☐ ☐☐

Q3. Ethnic group

1. White
2. Black Caribbean
3. Black African
4. Black other
5. Indian
6. Pakistani
7. Bangladeshi
8. Chinese
9. Other …
10. Other …

☐ *if 9 or 10 then please specify …* ..... *…Code →* ☐

Q4. Marital status

☐
1. Married
2. Cohabiting
3. Widowed
4. Separated
5. Divorced
6. Single

Q5. Dependents

a) Number of dependents (over 17) ☐

b) Number of children under 5 years ☐

c) Number of children aged 5–16 inclusive ☐

Q6. Accommodation status

1. Owner occupied
2. Council/housing association
3. Private rental
4. Job related
5. Lives with parents
6. Other …

☐ *if 6 please specify …* ..... *… Code →* ☐

Q7. Type of accommodation

1. Detached
2. Semi-detached
3. End-terrace
4. Mid-terrace
5. Flat/maisonette
6. Bedsitter
7. Hostel
8. Halls of residence
9. NFA
10. Other…

☐ *if 10 please specify …* ..... *... Code →* .....

Q8. Education

Q8a. Age left full-time education

☐☐

Q8b. Highest exam level *(see additional coding information for specific queries)*

0. None
1. CSE/NVQ Level 1
2. GCSE/O Level/NVQ Level 2
3. A level/BTEC/NVQ Level 3
4. HNC/HND/City & Guilds/Teaching qualification/NVQ Level 4
5. Degree/higher degree/NVQ Level 5
6. Vocational qualification

☐

If other, answer is unclear or unsure of level, enter here:

..... *If other, code →* ☐☐

Q8c. Still in education

1. No
2. Yes FT
3. Yes PT

If yes, course title

..... *If other, code →* ☐☐

☐

Q9. Occupation

Q9a. Economic position

1. Full time work
2. Part time work
3. Permanently sick/disabled
4. Unemployed
5. Retired
6. Student
7. Housewife
8. Voluntary work
9. Other

If yes, course title

If other, code →

Q9b. Patient's occupation

1. Currently employed
2. Main employment
3. Unemployed, last FT occupation

Number of people supervised

Function of organisation/nature of business

Q10. Partner's occupation

Q10a. Economic position

1. Full time work
2. Part time work
3. Permanently sick/disabled
4. Unemployed
5. Retired
6. Student
7. Housewife
8. Voluntary work
9. Other

If yes, course title

If other, code →

Q10b. Partner's occupation

1. Currently employed
2. Main employment
3. Unemployed, last FT occupation

Number of people supervised

Function of organisation/nature of business

Appendix 16

Date of onset and previous treatment information

Version 1
Dated 16/2/04

Date of Onset/Past Episodes and Treatment/Age of Initial Episode

1. When did you last feel well in spirits?

Years	Months

2. How long have you felt this bad?

Years	Months

3. Have you had depression like this before?

Once before ❑ Twice or more ❑ No ❑

4. How old were you when you first suffered from depression?

5. Have you had antidepressants before?

Yes ❑ No ❑

6. Were they successful?

- ❑ No previous antidepressants
- ❑ Unsuccessful because patient gave up
- ❑ Unsuccessful despite patient's perseverance for over a month
- ❑ Successful

Date completed: _____

Appendix 17

Shortened Life Events and Difficulties Schedule

Referral No. Randomisation ID.

Shortened LEDS interview for the THREAD study

Timepoint? Baseline ❑
26 weeks ❑

Date of interview

Now I would like to ask you about things that have happened to you and people close to you in the last year. The questions that I will ask you relate to core contacts, family members, confidants, and household members.

FOR ALL DIFFICULTIES, ESTABLISH WHEN THEY STARTED AND WHETHER THE LEVEL HAS CHANGED.

DATE OF ONSET OF MOST RECENT (OR CURRENT EPISODE OF DEPRESSION: _____

FRIENDS/CONFIDANTS

Is there anyone, either family or friends, that you feel very close to? Anyone else? (List at least the top 3 confidants) _____ _____ _____

If you had a problem of some sort, who would be the first person you would want to discuss it with? _____ _____ _____

Who else can you confide in about personal things or worries? _____ _____

Referral No. Randomisation ID.

Section 1: Illness

1. Have you or anyone in your family had any illness worse than colds or flu?

Yes No

(PROBE FOR LONG-TERM IMPLICATIONS: time off work, etc.)

1a. Has anyone been admitted to hospital or had an operation?

Yes No

(IF YES, PROBE: How serious was it? Was it an emergency?)

Has anyone else been ill?

Yes No

BOX A

FROM DOCTORS:
Reasons for illness
Chances of recovery/outlook/prognosis
Treatability
Future health: implications for work
Has anyone else had it in the family?
Lack of information from doctor
Shortcomings in care

IMPACT ON:
Employment: chance of losing job
Sick pay
Problems obtaining suitable care
Manifestations
Handicap: how needed to cut down
Pain, symptoms
How long in bed?
Interference with everyday life/hobbies/future plans
Had before? Outcome

ILLNESS OF OTHERS ONLY:
Was it expected?
How involved were you?
Nursing: infectiousness
Worry about dying
Worry about handicap
Diet: incontinence, lifting
Change in behaviour/personality (e.g. anger, irritability, ingratitude, blame)?
Stigma/embarrassment?

Referral No. Randomisation ID.

Section 2: Accident

2. Have you or anyone in your family had an accident (either a car accident, pedestrian, or at home?)

Yes No

(IF YES, PROBE: What happened? How serious was it?)

Section 3: Death

3. In the last year, has anyone close to you died?

Yes No

(PROBE: Was it unexpected? Were you involved at all?)

Has anyone attempted suicide?

Yes No

Has anyone died or nearly died?

Yes No

Section 4: Pregnancy

4. Have you, or has anyone in the family or among your close friends been expecting a baby or had a baby?

Yes No

(PROBE: Was it planned? Did the birth go smoothly?)

Section 5: Miscarriage

5. Any miscarriage, abortion or stillbirth?

Yes No

Referral No. Randomisation ID.

Section 6: Work

Have you or any household member been made redundant (laid off) or retired?

Yes No

(PROBE: Was it expected? Has it caused any financial problems?)

Section 6a: Work

6a. Have you or any household member been unemployed?

Yes No

(PROBE: For how long? Did it cause serious financial problems?)

Have you or any household member started a new job or had a major change at work in the last year?

Yes No

Have you had any problems at work over the last year that you have not already mentioned?

Yes No

BOX B

IF ANY IMPORTANT CHANGE ESTABLISHED, FIND OUT:
How it came about? Whose decision?
Financial implications
Convenience, hours, etc.

IF FOR PARTICIPANT:
Travel, babysitting, arrangements for children
Responsibility/demandingness
Interest, importance
Plans for future

Section 6b: Education

6b. Have you had any problems at school or college?

Yes No

Referral No. Randomisation ID.

Section 7: Money

7. Have you had any financial problems or been in debt?

Yes No

(PROBE: What about paying the rent, any difficulties with that? Have you had to cut down on expenditures?)

Section 8: Police/Court/Crime

8. Have you or anyone in your family had any contact with the police or lawyers or court?

Yes No

BOX C

Nature of offence
First time done it
First time in court
Other convictions
Verdict and sentence
Financial implications
What have other people said?
What have they said at work ?
Driving affected (if licence lost etc.)
Implications re: other people involved
Were you afraid they would try to get their own back?

Have you had any burglaries or a fire or flood?

Yes No

Has anything valuable been lost or stolen outside the house?

Yes No

Have you or anyone been attacked in the street or in the home?

Yes No

(PROBE: What happened? How serious was it?)

Referral No. Randomisation ID.

Anything else like that?

BOX D

How did it come about? (Participant's fault?)
Did you see the burglar?
How much was taken?
Problems with insurance?
Anything irreplaceable?
House damaged?

Section 9: Housing

9. Have you had any problems with your housing or neighbours?

Yes No

Have you had any changes regarding housing or neighbours?

Yes No

Any other housing problems?

BOX E

Why did you move? What happened?
Decision to move?
Were there any difficulties?
Have there been any difficulties since?
Expense
Consequences
Did you feel cut off? (Friends, babysitters, etc.)
New friends
Impact on job
Problems re: house/neighbours, etc.

Referral No. Randomisation ID.

Section 10: Social roles

10. Have you or anyone in the family become engaged or married?

Yes No

Has anyone broken off an engagement, been separated from their husband or wife, or been divorced?

Yes No

(IF YES, PROBE: Were you involved in any way?)

Anyone else married or divorced?

Yes No

BOX F

How long known?
Complications/delaying tactics/rejections
Family reactions
Was there anything about him/her that made you uneasy?

Have any of your children started or left school?

Yes No

Has anyone taken any important exams?

Yes No

(IF YES, PROBE: Did they go ok?)

Has anyone gone to University or started a new course?

Yes No

Anyone else with that sort of educational milestone?

Yes No

Referral No. Randomisation ID.

Section 11: Arguments/Relationship Difficulties

11. Have you lost contact with anyone who used to be close?

Yes No

PROBE FOR VCOs AND CONFIDANTS

Is there anyone (else) whom you see much less of than you used to?

Yes No

PROBE FOR VCOs AND CONFIDANTS

Have you ended any relationships in the last year?

Yes No

PROBE FOR VCOs AND CONFIDANTS

Have you had any other sort of crisis in the family (e.g. a major argument with a relative)?

Yes No

Have you made any new close friends in the last year (of either sex?)

Yes No

Any other new friends?

BOX G

Temporary? How long away?
How often seen before the change?
How much did you do together?
How often do you see each other now?
Distance
Telephone contact
How did you get along? How about now?
Preparation? Evidence rejection/guilt

INCREASE IN INTERACTION:
How fitted it – space/tension

Referral No. Randomisation ID.

Section 12: Marital

12. Have you had any problems in your marriage in the last year that haven't already been mentioned?

Yes No

(PROBE: Have you been separated for any length of time in the past year?
Do you manage to get time to do things together that you enjoy?
Do you often have arguments?
Has there ever been any violence between you?
What about the sexual side of things?)

Have you had any big disappointments in this time?

Yes No

Have you or anyone in the family had important news about something that is going to happen?

Yes No

(PROBE: Notice of layoff?

Moving?

BOX H

Reasons
Preparation/anticipation
Who left? What circumstances?
Forced to leave?
Anyone else involved?
Alternative relationship by either spouse?
Finance/housing
Custody
Children – their reactions, etc.
Clean break? Pestering? Violence?
Family's reactions?
Legal advice? When?
Maintenance arrangements
Often seen now

Referral No. Randomisation ID.

Section 13: Children

13. Have your children had any problems at school that you have not already mentioned (e.g. truancy) or have they been a problem at home?

Yes No

Do you worry about their friends?

Yes No

Any other problems with your children?

Section 14: Revelation

14. Sometimes people learn unexpected things about others close to them such as discovering their friend has been stealing, or their partner has been seeing someone else. Has anything like this happened to you?

Yes No

(PROBE: Something that changes your idea of a person's character?)

Anything else like that?

Referral No. Randomisation ID.

Section 15: Miscellaneous

15. Have you made any important decisions in the past year?

Yes No

Have you had to break any bad news?

Yes No

Section 16: Further miscellaneous

IF RELEVANT

A. (Foreign born)
Have you had any problems connected with living in this country?

Yes No

(PROBE: Immigrant visas, naturalization, change of name.)

B. (Canadian born)
Sometimes people experience discrimination of certain kinds on grounds of religion, colour, or disability. Have you had to face anything of this type at all in the last year?

Yes No

C. Now this is a bit of an odd question I'm afraid, but we do ask everyone:
Is there anything about yourself you feel self-conscious about?
Your appearance? The way you do things? Anything like that?
(If remotely relevant, probe for illiteracy)

Thank you for your time in completing this interview with me. I have asked you many questions, but when I review the interview, I may find that I missed asking important questions. Would it be alright to contact you by telephone if that is the case?

Appendix 18

Alcohol Use Disorders Identification Test (AUDIT)

Referral No: .....

Randomisation ID: .....

ALCOHOL CONSUMPTION AUDIT QUESTIONNAIRE

1. How often do you have a drink containing alcohol?

0. Never
1. Once a month
2. 2–4 times a month
3. 2–3 times a week
4. More than 4 times a week

☐

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

0. 1 or 2
1. 3 or 4
2. 5 or 6
3. 7 to 9
4. 10 or more

☐

3. How often do you have six or more drinks on one occasion?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

☐

6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily

☐

7. How often in the past year have you had a feeling of guilt or remorse after drinking?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily

☐

8. How often in the past year have you been unable to remember what happened the night before because you had been drinking?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily

☐

4. How often in the last year have you found that you were not able to stop drinking once you had started?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

5. How often in the last year have you failed to do what was normally expected of you because of drinking?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily

9. Have you or someone else been injured as a result of your drinking?

0. Never
2. Yes, but not in the last year
4. Yes, during the last year

10. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggest you cut it down?

0. Never
2. Yes, but not in the last year
4. Yes, during the last year

Adapted from Babor and Grant.[58]

Appendix 19

Bradford Somatic Inventory (BSI)

Referral No. Randomisation ID.

During the past month …

		YES (1)	NO (0)
1.	Have you had severe headaches?		
2.	Have you had fluttering or a feeling of something moving in your stomach?		
3.	Have you had pain or tension in your neck and shoulders?		
4.	Has your skin been burning or itching all over?		
5.	Have you had a feeling of constriction of your head, as if it was being gripped tightly from outside?		
6.	Have you felt pain in the chest or heart?		
7.	Has your mouth or throat felt dry?		
8.	Has there been darkness or mist in front of your eyes?		
9.	Have you felt a burning sensation in your stomach?		
10.	Have you felt a lack of energy (weakness) much of the time?		
11.	Has your head felt hot or burning?		
12.	Have you been sweating a lot?		
13.	Have you felt as if there was pressure or tightness on your chest or heart?		
14.	Have you been suffering ache or discomfort in the abdomen?		
15.	Has there been a choking sensation in your throat?		
16.	Have your hands or feet had pins and needles or gone numb?		
17.	Have you felt aches or pains all over the body?		
18.	Have you had a feeling of heat inside your body?		
19.	Have you been aware of palpitations (heart pounding)?		
20.	Have you felt pain or burning in your eyes?		
21.	Have you suffered from indigestion?		
22.	Have you been trembling or shaking?		
23.	Have you been passing urine more frequently?		

Referral No. Randomisation ID.

24.	Have you been having low back trouble?		
25.	Has your stomach felt swollen or bloated?		
26.	Has your head felt heavy?		
27.	Have you been feeling tired, even when you are not working?		
28.	Have you been getting pain in your legs?		
29.	Have you been feeling sick in the stomach (nausea)?		
30.	Have you had a feeling of pressure inside your head, as if your head was going to burst?		
31.	Have you had difficulty in breathing, even when resting?		
32.	Have you felt tingling (pins and needles) all over the body?		
33.	Have you been troubled by constipation?		
34.	Have you wanted to open your bowels (go to the toilet) more often than usual?		
35.	Have your palms been sweating a lot?		
36.	Have you had difficulty in swallowing, as if there was a lump in your throat?		
37.	Have you been feeling giddy or dizzy?		
38.	Have you had a bitter taste in your mouth?		
39.	Has your whole body felt heavy?		
40.	Have you had a burning sensation when passing urine?		
41.	Have you been hearing a buzzing noise in your ears or head?		
42.	Has your heart felt weak or sinking?		
43.	Have you suffered from excessive wind (gas) or belching?		
44.	Have your hands or feet felt cold?		
Men only			
45.	Have you had difficulty getting a full erection?		
46.	Have you felt that you have been passing semen in your urine?		

Thank you for your co-operation.

Adapted from Mumford *et al.*[51]

Appendix 20

Symptom attribution questionnaire

Referral No: .....

Randomisation ID: .....

Version 1 dated 16/2/04

Symptom Attribution

The following question asks you about your symptoms.

PLEASE TICK ALL BOXES THAT APPLY TO YOU

	Physical cause	Stress or emotional cause	Don't know
What do you think are the causes of your symptoms?	❑	❑	❑

Tick ONE OR MORE boxes

Appendix 21

Patient preference questionnaire

Referral No:

Randomisation ID:

Version 1 dated 16/2/04

Patient Preference

As you will have read in the information sheet, you will be randomly allocated to either the group that receives fluoxetine or the group that does not.

IF you had a choice, which group would you prefer to be in?
(Please tick one box)

1	Supportive Care without Fluoxetine (Prozac)	❑
2	Supportive Care with Fluoxetine (Prozac)	❑
3	No Preference	❑

Appendix 22

Care received questionnaire

Referral No. Randomisation ID.

Care Received from your Doctor(s) **Follow-up:**

We recognise that it is not always possible or necessary for doctors to do all the things mentioned. Please think about the GP(s) you have seen most since being part of the study.

1 Did your doctor(s) discuss practical problems which have been facing you? (For example: problems at work, at home, with family responsibilities, housing, or money worries.)

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

2 Did the doctor(s) discuss with you ways in which you could work to solve the problems facing you?

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

3 Did the doctor(s) discuss whether you should do more physical exercise?

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

4 Did the doctor(s) discuss whether you should do relaxation exercises?

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

5 Did the doctor(s) discuss whether you could find more leisure time for yourself?

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

6 Did the doctor(s) discuss the possibility that you could start or restart activities which you might enjoy?

- No ❑
- Yes a little ❑
- Yes a lot ❑
- I can't remember ❑

Referral No. Randomisation ID.

7 Did the doctor(s) discuss addressing your relationships with friends, family, or loved ones?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

8 Did the doctor(s) discuss whether you could talk things through with trusted family or friends?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

9 Did the doctor(s) discuss referring you for counselling, psychology treatment, or talking treatments?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

10 Did the doctor(s) discuss with you the possibility of changing your work patterns?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

11 Did the doctor discuss whether the way you think about things could be changed to improve your symptoms?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

12 Did the doctor discuss antidepressant medication with you?

No ❑
Yes a little ❑
Yes a lot ❑
I can't remember ❑

13 Have you been prescribed antidepressants? Yes ❑ No ❑

Referral No. Randomisation ID.

You only need to complete the following questions if you have answered YES to Question 13 above and you have been prescribed antidepressant medication by your doctor.

We realise that there are lots of reasons why people do not like taking antidepressants and sometimes do not take the antidepressant medication which is prescribed to them. We are interested in your experience. If you have been prescribed antidepressant medication, please list below what it was and how long you have taken it for. If you have taken more than one please write down which ones they were and for how long.

14 How many weeks did you actually take your medicine for during the past 12 weeks? *(Do not worry if you cannot recall the name of the medicine.)*

Antidepressant medication

Name ……
Taken for …… week(s)

15 Do you ever forget to take your medicine?
Yes ❑ No ❑

16 Are you careless at times about taking your medicine?
Yes ❑ No ❑

17 When you feel better do you sometimes stop taking your medicine?
Yes ❑ No ❑

18 Sometimes if you feel worse when you take the medicine, do you stop taking it?
Yes ❑ No ❑

19 Have you suffered any side-effects from the medication? Yes ❑ No ❑

20 If yes, what were these?
.....
.....

Date completed:

Appendix 23

Adverse events

26-week study period	Treatment arm	Event no. and date	Type of event	Brief description	Comments	Centre and PCT	Reported
24/11/04–25/5/05	SSRI plus supportive care (fluoxetine) 30/11/04 (30 tabs) 10/1/05 (56 tabs) 23/5/05 (56 tabs)	1 11/3/05	SAE	Paracetamol overdose, overnight hospitalisation required	No impact for patients in trial	Southampton Southampton City	Discussed at Study Group Copies of report sent to the Chairs of TSC and DMEC Included in progress report to HTA (Sept 05) and annual safety reports to MHRA and MREC
22/2/05–23/8/05	SSRI plus supportive care (fluoxetine) 23/2/05 (28 caps) (citalopram) 11/3/05 (14 tabs) 15/8/05 (28 tabs)	2a 28/2/05	AR	Uncontrollable shaking (dyskinesia)	Recognised side effect	Liverpool Central Liverpool	Discussed at Study Group Copies of report sent to the Chairs of TSC and DMEC Included in progress report to HTA (Sept 05) and annual safety reports to MHRA and MREC
		2b 12/5/05	AE	Admission to hospital for evacuation of retained products of conception (ERPC) following miscarriage but discharged the same day	Patient stopped medication on realising that she was pregnant. No impact for patients in trial		Discussed at Study Group Copies of report sent to the Chairs of TSC and DMEC Included in progress report to HTA (Sept 05) and annual safety reports to MHRA and MREC
		2c 20/7/05	SAE	Admission to hospital for lateral release right knee ligaments	Not study related so no further action required		Discovered through patient records on 31/7/06 (not previously accessed as preference patient). Will be included in HTA report (Sept 06) and annual safety reports to MHRA and MREC
17/1/05–21/7/05	Supportive care alone	3 13/3/05	SAE	Died from rapid widespread cancer	No medication involved. Not study related so no further action taken	Southampton New Forest	No medication involved. To be reported in annual safety reports to MREC, HTA and MHRA
23/8/05–23/3/06	SSRI plus supportive care (fluoxetine) 26/9/05 (30 tabs)	4a 12/3/06	SAE	Admission to hospital for ERPC following miscarriage	Patient only took medication for 30 days and was not taking medication at time of conception. Event not related to study	Southampton S Wiltshire	Discussed at Study Group Copies of report sent to the Chairs of TSC and DMEC (19/7/06) To be reported to MREC, HTA and MHRA in regular reports

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26-week study period	Treatment arm	Event no. and date	Type of event	Brief description	Comments	Centre and PCT	Reported
		4b 18/3/06	SAE	Admission to hospital for septic arthritis in the knee	Event not related to study		To be reported to MREC, MHRA and HTA (Sept 06) in regular reports
5/4/06–5/10/06	SSRI plus supportive care (citalopram) 6/4/06 (28 tabs)	5 15/4/06	AR	Pains in spine, arms and head	Recognised side effect. No impact for patients in trial	Southampton Guildford & Waverley	Discussed at Study Group Copies of report sent to the Chairs of TSC and DMEC (19/7/06) To be reported to HTA (Sept 06), MREC and MHRA in regular reports
27/4/05–26/10/05	Supportive care alone	6 12/8/05	SAE	Hospitalisation for planned operation for arthritic foot	Not related to the trial so no further action required	Southampton Bournemouth	Reported to HTA (Sept 06), MREC and MHRA in regular reports
7/4/06–6/10/06	SSRI plus supportive care (fluoxetine 20 mg) 8/6/06 23/6/06 6/7/06 6/9/06	7 26/5/06	SAE	The patient took an overdose of paracetamol and ibuprofen and was taken to A&E	No impact for patients in trial. Further investigation revealed that no medication was prescribed before the event	London Lewisham	Reported to Study Group (20/11/06) and HTA in regular progress report (1/3/07)
14/8/06–14/2/07	SSRI plus supportive care (fluoxetine 20mg) 16/8/06 30/8/06 19/9/06	8 30/8/06	AR	The patient described hot skin, red face, unable to drive and a 'bad head'	The patient had been prescribed fluoxetine 20 mg daily. No impact for patients in trial	Liverpool Bolton	Reported to Study Group (20/11/06) and HTA in regular progress report (1/3/07)
8/2/06–9/8/07	SSRI plus supportive care (citalopram, sertraline, velafaxine, fluoxetine)	9 15/2/07	AR	Patient reported sedation, nausea and headache	Recognised side effect. No impact for patients in trial	Southampton Fareham & Gosport	Reported to Study Group (18/6/07) and reported to HTA in regular progress report (Sept 07)

Appendix 24

Unit costs used in economic evaluation

Service	Unit cost	Source
Inpatient admission	£471 per day	NHS Reference Costs
Outpatient consultation	£108 per attendance	NHS Reference Costs
Day patient	£108 per attendance	NHS Reference Costs
A&E consultation	£91 per visit	NHS Reference Costs
GP surgery consultation	£22 per consultation	PSSRU
GP telephone contact	£23 per consultation	PSSRU
GP home visit	£49 per visit	PSSRU
Practice nurse contact	£10 per contact	PSSRU
District nurse contact	£61 per hour	PSSRU
Community mental health nurse contact	£72 per hour	PSSRU
Other nurse contact	£47 per hour	PSSRU
Health visitor contact	£84 per hour	PSSRU
Counsellor contact	£48 per hour	PSSRU
Psychologist contact	£66 per hour	PSSRU
Occupational therapist	£57 per hour	PSSRU
Social worker contact	£77 per hour	PSSRU
Housing worker contact	£77 per hour	PSSRU
Community support worker	£69 per hour	PSSRU
Day centre attendance	£23 per attendance	PSSRU
Physiotherapist	£40 per hour	PSSRU

PSSRU, Personal Social Services Research Unit, University of Kent.
Complementary health care was costed according to prices paid by patients.
Medication was costed according to *British National Formulary* prices per drug.

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We look forward to hearing from you.

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