TITLE **Reference : 06/05/01**

Projected start date: 1-12-2009

IMPACT: Improving Mood with Psychoanalytic and Cognitive Therapies

A Randomised Controlled Relapse Prevention Trial of Short Term Psychoanalytic Psychotherapy (STPP), Cognitive Behaviour Therapy (CBT) and Specialist Clinical Care (SCC) in adolescents with moderate to severe depression attending routine child and adolescent mental health clinics.

Background

Importance of depressive disorder in young people

Major depression in adolescents is an important problem for the NHS. Around 1 in 10 referrals to child psychiatrists have significant depressive conditions(R. C. Harrington, Fudge, Rutter, Pickles, & Hill, 1990). Clinical cases have many social and cognitive impairments (Park et al., 2005; Puig-Antich, Kauffman, & Ryan, 1993; Wilkinson & Goodyer, 2006) and significantly increased risks of both attempted and completed suicide (Myers, McCauley, Calderon, & Treder, 1991; Rao, Weissman, Martin, & . 1993), and a high rate of recurrence in adulthood (Dunn & Goodyer, 2006; Fombonne et al., 2001; R. C. Harrington et al., 1990). Indeed, it seems that around 30% of adult affective disorders start in adolescence. A reduction in the duration and number of episodes in adolescence could therefore not only reduce short-term morbidity but also help to prevent depressive conditions and suicidal behaviour later in life(R. C. Harrington & Clark, 1998).

Treatments for adolescent major depression

Cognitive behaviour therapy has been most widely investigated and shown to be effective in mild to moderate depressions in the short term (R. Harrington, Whittaker, Shoebridge, & Campbell, 1998; Weersing, Iyengar, Kolko, Birmaher, & Brent, 2006). Recent studies of moderate to severe depression have shown that combination of fluoxetine and CBT produces significantly greater improvement at 12 weeks than CBT alone (Clarke et al., 2005; March et al., 2004). As yet there is no study that has determined medium- to longer-term effects of psychological treatment on remission in the medium term and/or subsequent relapse. The evidence is that patients will begin to relapse within 3 months of discharge, even in those with effective acute treatment, and over the next 5-10 years between 50%-70% will relapse (Dunn & Goodyer, 2006). It is essential to determine which treatments are most effective in facilitating remission between 28 and 52 weeks and relapse prevention in the 12 months following entry into remission.

There is a limited evidence base for STPP. There are relatively few randomized controlled trials of psychodynamic psychotherapy (Robin et al., 1999; Sinha & Kapur, 1999; Smyrnios & Kirkby, 1993; Trowell et al., 2007; Trowell et al., 2002). All but one of these trials contrasted individual child psychotherapy with another (evidence-based) treatment for disorders that included but, with one exception, were not focused on major depression. In addition several studies employed quasi-randomized methods of assignment such as postcode (Moran, Fonagy, Kurtz, Bolton, & Brook, 1991)or therapist vacancy (Muratori et al., 2003; Muratori et al., 2001). Six studies reported on findings with matched comparison groups (Fonagy & Target, 1994; Heinicke & Ramsey-Klee, 1986; Reid, Alvarez, & Lee, 2001; Target & Fonagy, 1994a, 1994b). A further two studies report non-matched control groups (Apter, Bernhout, & Tyano, 1984; Boston & Lush, 1994). Two further studies used an untreated but poorly matched control sample (Lush, Boston, & Grainger, 1991; Target & Fonagy, 2002). In addition there are a number of open trials of child

psychotherapy employing no comparison groups (Baruch, Fearon, & Gerber, 1998; Fonagy & Target, 1996b; Petri & Thieme, 1978; Vilsvik & Vaglum, 1990; Winkelmann et al., 2000). As these studies did not target depression they are at best suggestive of the relevance of STPP for this disorder. The AFC chart review study of 763 patients (Target & Fonagy, 1994a)included 65 children and adolescents with major depression, who had been treated in long term psychodynamic therapy. By the end of therapy, over 75% showed reliable improvement in functioning and no depressive symptoms. There was a clear dose-response relationship with treatment intensity and length of treatment both predicting remission after controlling for level of impairment at referral. Childhood depression has been shown to be susceptible to a brief individual psychodynamic psychotherapy in a multicentre European trial (Trowell et al., 2007). At seven-month follow-up none of the moderately to severely depressed young people met criteria, which is comparable to children treated with a combination of fluoxetine and CBT (Goodyer et al, submitted). The presence of anxiety or dysthymia signalled particular suitability for individual treatment and comorbidity with ODD or CD contraindicated it.

Why study the longer term effects of treatment on remission and relapse of depression?

The HTA brief specifically states that the primary outcomes for the study should be recurrence or persistence of symptoms by 52 weeks and cost effectiveness. Major depression (MD) in adolescents is associated with significant recurrence, relapse and even persistence into adult life (Dunn & Goodyer, 2006; R. C. Harrington & Dubicka, 2001). Treatment studies to date have focussed exclusively on the ability of treatments to effect remission in the 3-6 month period after treatment initiation (Brent et al., 1997; Clarke et al., 2005; March et al., 2004). In addition all studies have tested rather specialised treatments including cognitive behaviour therapy, interpersonal therapy and SSRIs. No study has examined active multidisciplinary clinical care as commonly practised in the tier 3 CAMHS within the NHS. Furthermore the short-term nature of studies to date has prevented us from examining medium- to longer-term effects of treatments on reducing persistent disorder and diminishing risk for relapse. For example, it has not been possible to distinguish non-responders from slow and late responders because of short-term cessation of trials. Neither has it been possible to determine the effects of treatment on relapse. All treatment studies identify hard-to-treat sub-groups which invariably include those with multiple non-depressive comorbidity, suicidal ideation and high impairment at entry (Brent, Kolko, Birmaher, Baugher, & Bridge, 1999; Dunn & Goodyer, 2006). These cases are invariably classified as non-responders at 12-20-week follow-up. This may underestimate the impact of treatments on severe cases seen routinely in CAMHS. It is equally plausible that short-term high-intensity psychological treatments delivered over less than 16 weeks may be too brief to effect remission and/or prevent relapse. The fact that some of these cases show little or no response by 12-28 weeks does not mean they are treatment resistant. Response may take longer to emerge as has been shown in longitudinal follow up studies of adult patients who have received CBT where effects may not emerge fully until 12 months after treatment and longer psychotherapy may diminish relapse and the use of antidepressants (Fava et al., 2004; Paykel et al., 2005). There is also some evidence for psychotherapy effects emerging over 12 months in children with emotional disorder who received more intensive dynamic psychotherapy than used hitherto in trials of depressed young people (Muratori, Picchi, Bruni, Patarnello, & Romagnoli, 2003; Muratori et al., 2001). In severe cases in particular psychological treatment may have been given at the wrong dose and therefore minimised the likelihood of response in short or medium term (Weiss, Catron, & Harris, 2000). We plan to study the effects of treatments on persistence and relapse in the medium term, i.e. over the 18-month follow-up period. In this study we will randomize all cases who meet criteria at referral.

Why study the effects of a specialist versus a more general treatment?

The commissioning brief calls for research on the clinical and cost-effectiveness of 2 specialist psychological treatments [CBT or STPP] against treatment as usual in moderate to severe patients with depression attending CAMHS. This clinical population is markedly unwell (Dunn & Goodyer, 2006) with significant risk of self harm, suicide risk substance misuse and chronicity. Management of such cases is worrisome for the responsible clinical team. Tier 3 clinicians will not pass such cases into the trial unless the study team can be demonstrably competent and responsive in its care and with its therapeutic skills. The study team must be capable of providing specialist treatment, which requires the kind of personnel structure we have outlined.

Clinicians regard psychosocial approaches as best first-line practice for treating depression

The NICE guidelines for the treatment of unipolar depression recommend psychosocial approaches as the first line of treatment. There was insufficient evidence for NICE to recommend a specific form of therapy. General psychosocial approaches were recommended in the first instance and if no improvement within 4-12 weeks a specialised treatment such as CBT should be introduced.

Specialist Clinical Care as active therapy

No studies have examined whether active clinical care in specialist CAMHS, referred to as Specialist Clinical Care (SCC), with up to 12 sessions [i.e. low-intensity treatment], together with fluoxetine, is less effective in relapse prevention than a specialist psychological treatment delivered weekly for up to 20 sessions or more [i.e. higher-intensity treatment]. The only UK RCT of adolescent depression conducted in CAMHS clinics has shown that SCC (specialist clinical care) + fluoxetine is as effective as SCC + fluoxetine + CBT in effecting remission at 28 weeks (Goodyer et al., 2007). This finding supports prior research showing that SCC may be the treatment of choice in the first instance with fluoxetine added if there is no clinical response. All CAMHS are able to deliver SCC through multidisciplinary teams. In contrast, CBT and STPP specialists are not available to many services. The NICE guidelines strongly recommend that specialist therapies should be available to children and young people with moderate or severe depression. Given the expenditure that will be entailed in the provision of these specialist therapy services as the guidelines are nationally implemented it is urgent and essential that we establish whether the latter are more effective and cost effective than SCC + Fluoxetine in the medium term.

Why question the value of specialist therapies and include STPP in the evaluation?

On the bases of thorough explorations of the evidence base, CBT has been recommended as the treatment of choice in current national plans to improve SCCess to psychological therapies (Care Services Improvement Partnership (CISP, www.csip.org.uk 2006); (Layard, 2006)). In depressed young people attending outpatient services CBT alone may be less effective in producing remission than previously considered. Effect sizes associated with the provision of short term CBT have been small in both efficacy and effectiveness studies (Asarnow et al., 2005; Clarke et al., 2005; March et al., 2004). Two strategies are called for: (1) intensification of the CBT provided to young people with moderate and severe depression both in terms of number of sessions and the length of overall treatment. This approach has met with some success in adults with major depression (Paykel, 2006; Scott, Palmer, Paykel, Teasdale, & Hayhurst, 2003; Scott et al., 2000)(2) Broadening the range of treatments offered to young people with moderate and severe depression. The two realistic candidates for such expansion are systemic family therapy and individual psychoanalytic psychotherapy. Neither treatment can be considered well established in terms of evidence base (Roth & Fonagy, 2004; Weisz, 2004) but both deserve systematic inquiry. A previous relatively large scale RCT has demonstrated systemic family therapy to be less effective then CBT (Brent et al., 1999). A more dynamic therapy, also delivered as a brief 12-16 week treatment, focussing on relational difficulties and self-perceptions [interpersonal psychotherapy, IPT] has shown promising

efficacy in mild to moderate depressions in the community (Mufson et al., 2004; Young, Mufson, & Davies, 2006). As yet there are no studies of IPT in the moderate to severe adolescent depressed populations. IPT is rare in current practised in the NHS. The short term psychoanalytic psychotherapy [STPP] commonly provided in UK CAMHS is practised by child psychotherapists. There is evidence for efficacy of this treatment in childhood emotional disorders seen in CAMHS that consist of patients with anxiety disorders and some concurrent depressive symptoms (Fonagy & Target, 1996a; Target & Fonagy, 1994a) In a recent European multisite study STPP was found to be a relatively effective treatment in the short term for moderate depression in a somewhat younger groups of patients (Trowell et al., 2007). While widely practiced particularly in certain regions of the country(Beedell & Payne, 1987; Rance, 2003; Sherwin-White, Shuttleworth, Tydeman, & Urwin, 2003) it is unclear whether this costly therapy is effective let alone cost-effective in the treatment of moderate to severe depression in the sense of effecting a greater rate of remission or reducing the risk of relapse. Thus we do not know whether either specialist treatment would reduce relapse compared to ongoing SCC + Fluoxetine, in the medium term.

Why study reduction in relapse rates as well as treatment effects on remission

In the UK ADAPT study 44% of cases were not in remission by 28 weeks and a further 20% were no better. These findings highlight the problem of cessation of a psychosocial treatment trial in the short term. Naturalistic longitudinal studies have shown that recovery for those exposed to active clinical care including family therapy and fluoxetine may vary from a few weeks to 18 months in a few cases with around 80% remitted at a year (Dunn & Goodyer, 2006; I. M. Goodyer, Herbert, & Tamplin, 2003; Park, Goodyer, & Teasdale, 2005) . This suggests the need for follow-up in the medium term to evaluate the best estimate of treatment effects on remission. A medium-term follow-up of 18 months will also allow for an evaluation of relapse rates, as these can occur within a few weeks of remission being achieved (R. C. Harrington & Dubicka, 2001) . There is evidence for the effectiveness of CBT in relapse prevention in adults with a history of unipolar depression, although there is also an increase in costs (Paykel, 2006) (Scott et al., 2003). Relapse prevention in adolescents may reduce the serious effects of depressive disorder including educational failure, suicide, substance misuse and chronic mental illness (Dunn & Goodyer, 2006; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001). Establishing an active treatment that reduces the recurrence risk into adult life would therefore decrease adult morbidity and costs to the NHS.

Which treatment is likely to be most effective and cost effective?

There are no studies in adolescents or adults that compare the effectiveness and cost effectiveness of specialist treatments to each other. On the basis of previous studies in adolescence we predict that time to remission will be no different between the 3 treatments as there is no evidence to show a differential effect on reduction in symptoms in the short term between treatments (Goodyer et al., 2007; March et al., 2004). The key question in the HTA brief is however to determine treatment effectiveness and cost effectiveness on recurrence or persistence of symptoms. There is evidence from the adult literature that residual symptoms are associated with relapse but can be reduced in the medium term (52 -86 weeks) with CBT (Paykel, 2006) although there may be an increase in treatment costs as a result. Similar later effects may occur for STPP especially in higher dose therapies (Muratori et al., 2003; Muratori et al., 2001). STPP in particular may contain sleeper effects as indicated by continued reduction of symptoms by 2 years (Muratori et al., 2003) with active psychodynamic treatment compared to low intensity community services. The current findings are not conclusive of superiority effect for CBT over STPP in the medium term [52-104 weeks]. Only STPP has modest evidence for sleeper effects in young people. We therefore will design the study with a 2 level hypothesis: i) Both CBT and STPP will show superiority effects compared to SCC in the primary outcomes at 52 and 86 weeks ii) CBT will show non inferiority effects to STPP at 52 weeks iii) STPP will show superiority effects compared to CBT at 86 weeks.

In terms of cost-effectiveness, the only evidence available comes from the ADAPT study, which does not support the hypothesis that the additional cost of specialized interventions for adolescents with depression can be justified in terms of reductions in costs elsewhere or improvements in outcome (Byford et al., 2007). It is possible that the ADAPT study, with only a 28-week follow-up, was not long enough to pick up changes that specialist therapies may have in the medium to long-term. This may be particularly true of STPP which is a longer intervention than CBT or SCC. The proposed study will help to clarify this.

PLANNED INVESTIGATION

Overview (see the figure at the end of this annex)

We plan a superiority trial that compares Specialist Clinical Care [SCC], with Cognitive Behaviour Therapy [CBT] and Short Term Psychoanalytic Psychotherapy [STPP] to reduce persistent disorder and relapse in adolescents with DSM IV defined moderate to severe Major Depression. Cases with MD will be randomly allocated to SCC, CBT or STPP. Outcomes will be assessed at 6, 12, 28 and 52 and 86 weeks by outcome assessors unaware of treatment allocation.

Research questions, hypotheses and objectives

Questions and hypotheses

The broad question is 'What is the clinical and cost-effectiveness of psychological treatment in reducing persistence and/or recurrence in the medium term for major depression in adolescents?' We believe that the key pragmatic issue for the NHS is whether specialist psychological treatments are more effective at reducing persistent and/or relapsing disorder in the medium term than general active clinical care. We have a superiority hypothesis which will test whether:

i) Both CBT and STPP will show superiority effects compared to TAU in the primary outcomes at 52 and 86 weeks
ii) CBT will show non inferiority effects to STPP at 52 weeks
iii) STPP will show superiority effects compared to CBT at 86 weeks.

In terms of cost-effectiveness, we will explore the hypothesis that the additional costs of specialised treatment are justified by improvements in effectiveness, and possibly decreased use of health and social care services in the medium term.

We also want to determine whether the treatments differ a) in user satisfaction, and b) within subgroups defined by severity.

Objectives

1. To confirm recruitment of 18 NHS CAMHS clinics in 3 regions into the study and set up virtual clinic (mo. 1-6).
2. To train outcome assessors to a predetermined level of reliability and therapists to a pre-determined level of competence (mo. 6).
3. To identify a representative clinical sample of 600 adolescents with moderate to severe MD (from mo. 6).
4. To randomize 510 cases to the interventions (by mo. 24).
5. To assess outcomes of >90% of randomized cases at 6, 12 and 28, 52 and 86 weeks later (mo. 48).
6. To estimate the total cost of all hospital and community health and social services, and the cost of schooling and education sector support services. (mo. 54).
7. To identify the key cost and outcome drivers and to explore the relative cost-effectiveness of the interventions (mo. 54).
8. To analyse data, write reports and prepare a paper for publication in a peer-reviewed journal (mo. 66).

Planned interventions

Treatment principles

This is a superiority trial that seeks to evaluate the treatments that would be used in NHS practice. We shall therefore employ comprehensive treatment protocols but these will not be as extensive as those that might be used in explanatory trials. We shall use treatment manuals as a) it has been our experience that these aid dissemination of treatment methods into clinical practice, b) they help to standardize the intervention between therapists and across sites, and c) they form the basis for audiotape ratings of adherence to the intervention. If our trial is to influence the field, we will have to demonstrate that the interventions have been conducted competently.

Overview of training and supervision procedures for the therapists

The specialised psychological treatments will be carried out by professionals qualified in the 2 modalities. Each will be supervised in their region by senior CBT and STPP therapists respectively.
The treatment manuals specify how 'competence' is defined. The trial interventions will be carefully monitored and supervised using several procedures. First, at each site the therapist will obtain regular clinical supervision. Second, all therapy sessions will be audiotaped and a random sample rated for adherence to the manual and competence in giving the therapy. CBT will be evaluated using parts of a standardized system of known reliability and validity, the Collaborative Study Psychotherapy Rating Scale (Hill, O'Grady, & Elkin, 1992) (CSPRS). The CSPRS was used in a large multicentre American study of the treatment of adult depression, which compared psychological therapies (including CBT) and medication. A similar procedure will be undertaken for STPP using a well-validated and extensively used Q-sort rating of adherence in adult psychodynamic psychotherapy (Jones, 2000)recently extended for use with treatments for young people (Schneider and Midgley, in press) and for SCC using the Cambridge clinical care scale derived from the previous ADAPT study. The rating of audiotapes should help to ensure that the interventions are given properly and, importantly, that therapists in the SCC group do not give cognitive-behavioural or psychodynamic interventions. Around 800 therapy sessions (≅ 4/case) would be rated over three years by Fonagy and Target for STPP, Verduyn and Reynolds for CBT and Goodyer, Dubicka and Kelvin for SCC (around 70/rater/year). Biweekly conference calls will be held between the three centres to discuss therapy and to make decisions about, for instance, exclusion from the trial. Quality control meetings between the 3 centres will be held bi-monthly. Fluoxetine will be prescribed to any case in any arm that meets defined prescribing criteria determined by level of severity, degree of psychosocial impairment, and lack of response to psychological treatment after 6 sessions.

Therapists

At each centre a child psychiatrist will be responsible for general co-ordination of cases from the 6 clinics, supervising the medication and for conducting most of the SCC. The 2 research therapists will be responsible for the specialist treatment.
The three treatments will be delivered at different levels of intensity, defined as the total number of sessions over the study period + level of psychological work, as follows: i) low intensity specialist clinical care SCC that is primarily advice and support [12 sessions]; medium intensity CBT [20 sessions]; high intensity STPP [30 sessions].

Specialist Clinical Care [SCC]

SCC will consist of a psychosocial management programme together with the opportunity to add fluoxetine in severe cases: The procedure will be a treatment course consisting first of 6 sessions over the first 8 weeks. If remission is not achieved psychosocial treatment will be extended for a further 6 sessions and fluoxetine added. Total treatment time will be 16 weeks with a 1-session follow up at 20 weeks. The content will involve a conversational approach with the patient and

their parents and siblings if required. The treatment will emphasise the importance of action-oriented, goal-focussed and interpersonal activities as therapeutic strategies. There will be no focus on changing cognitions. Neither will negative cognition driven behaviours be deconstructed. Finally there will be no ongoing analysis with the patient about the putative unconscious origins of their symptoms. The first 2 sessions will consist of: assessment and formulation resulting in explanation and description of the features and natural history of the condition followed by advice on general mental hygiene and dispelling incorrect perceptions and beliefs about depression [e.g. they grow out of it; children cannot get depressed]. Sessions 3 to 6 will consist of monitoring progress and mental states; continuing explanation and clarification of the disorder including explaining symptoms of distorted thinking, anhedonia and withdrawal; dealing with worries regarding pace of improvement. Advice will be given on personal activities, social behaviour, and school work and attention will be paid to immediate distressing events such as family difficulties. There will be a continuing focus on psychoeducation, i.e. what depression is / comorbid diagnoses / how common it is / its nature and the typical course of the disorder / how it affects the adolescent and those around them. Sessions 7 through 12 will continue within the above framework. More detailed attention will be paid to the consequences of any acute undesirable life events focussed on the adolescents. Up to 4 family or marital therapy sessions for parents will be given where required. Liaison with external agencies and personnel e.g. teachers, social care and peer group will be undertaken. Specific advice will be given on mental and physical hygiene. Developing a confiding relation with an important other will be facilitated. Helping oneself through engaging in pleasurable activities and diminishing solitariness will be strongly enforced. SCC will not use cognitive or reflective techniques related to analysis of unconscious motives and behaviours nor specific behavioural strategies. After 6 sessions patients who are not in remission will be offered Fluoxetine as a component of SCC to be taken for the next 12 weeks. Very ill patients may require Fluoxetine before 6 sessions have been delivered

Cognitive behaviour therapy (CBT)

CBT therapy in this trial is based on that developed for adults and has been adapted in terms of parental involvement and specific techniques to be suitable for adolescents. The form of CBT that will be given has already been shown to be effective in a randomized trial (Wood, Harrington, & Moore, 1996). CBT is an active, verbal therapy which is based on an individual formulation of the client's current problems and their associated antecedents, precipitating and maintaining factors. This formulation is shared with the client (and their parents). CBT is typified by an emphasis on 'collaborative empiricism', explicit, tangible and shared goals and clear structured sessions. Typically therapy has a number of phases which include assessment, psycho-education into the cognitive behavioural model of depression (e.g. the links between thoughts, feelings and behaviours), the introduction of monitoring methods (e.g. mood, behavioural and thought monitoring), behavioural activation and activity scheduling, linking thoughts, feelings and behaviours, identifying and challenging negative automatic thoughts, developing and reinforcing adaptive thoughts and relapse prevention strategies.

Specific techniques have been developed to support therapy and to maintain engagement and optimism for change. Topics introduced within therapy session are extended and supported outside the session by tasks completed by the client between sessions and reviewed at each subsequent session. For example, a client who had negative thoughts about their performance in social encounters might have the task of setting up a specific social encounter and monitoring their thoughts and feelings as well as their actual performance in the feared (and usually avoided situation).

The structuring of CBT sessions is reflected also in the structure of therapy overall. Specific contracts are establishes at the outset of therapy between the client and the therapist around such matters as the timing and location of sessions, the total number of sessions to be offered and how

this will be reviewed, and the expectations of therapist and client of each other (e.g. limits of confidentiality and how risk will be managed). The programme would be given weekly for 12 weeks, followed by 8 biweekly sessions until the end of the study. It is mainly an individual therapy, but there is also much parental involvement. It was developed as a *pragmatic* therapy that would be SCCeptable to depressed adolescent patients and that could be learned quickly by child mental health professionals working in the NHS.

Short term Psychoanalytic Therapy (STPP)

The form of STPP to be used in the trial is a combination of two specially developed treatment manuals. The core of the intervention will be based on a manual developed by Marie Rhodes and Judith Trowell (unpublished) at the Tavistock Clinic, where the majority of currently practicing STPP therapists in the UK have obtained their training. This treatment manual is specifically aimed at offering STPP for young people with depression and it was recently validated in a multisite trial. In order to enhance the generalisability of the treatment protocol, this manual has been expanded and integrated with the treatment manual that has evolved out of clinical work at the Anna Freud Centre (Fonagy, Miller, Edgcumbe, Target, & Kennedy, 1993; Sandler, Kennedy, & Tyson, 1980)This manual has been the focus of considerable empirical work (Miller, 1993)and a Dutch and Canadian version of the manual are currently in use in RCTs in these countries. While the Tavistock manual is organised around aspects of STPP that focus principally around interpretation of unconscious conflict and insight, the AFC manual is primarily concerned with helping young people overcome developmental problems using more supportive and less expressive strategies. The AFC manual focuses on developmental delays and distortions in children with severe psychological problems and identifies specific therapeutic techniques for offering developmental help' to these children in line with the developmental needs identified. Both approaches make extensive use of modern attachment theory and the concepts of internal working models and aim to elaborate and increase the coherence of the young person's maladaptive mental models of attachment relationships and thereby improve their capacity for affect regulation (Fonagy, Gergely, Jurist, & Target, 2002). The comprehensive implementation of STPP also involves some family work which is also guided by a treatment manual. STPP will be delivered weekly for 30 weeks.

Use of Fluoxetine

Fluoxetine will be part of the treatment described within the SCC manual and available to any patient who has not responded to 6 sessions of active clinical care. Patients receiving CBT or STPP may also be prescribed fluoxetine if they demonstrate active suicidal or psychotic symptoms at assessment that remain not responsive to 4 sessions of psychological treatment. Very ill patients may require Fluoxetine before 4-6 sessions have been delivered

The initial dosage will be 10 mg (as syrup) increased to 20 mg once a day, if there are no side effects. If there is no response by 6 weeks the dose will be increased to 40mg. The medication will be monitored by the research child psychiatrist over the trial period. Compliance will be monitored by counting returned pills/syrup bottles (in NHS practice frequent blood tests would not be SCCeptable and assays of SSRI levels are seldom available).

Monitoring adverse effects of the interventions

All subjects will have a full medical history and examination at the start of the study. Blood biochemistry will be obtained only when indicated clinically. In all groups there will be regular clinical assessment of the presence of possible side effects from the medication. These will be specified in the treatment manual. Although it is often assumed that psychological interventions can only do well, some patients find such treatments too intrusive, or upsetting. Adverse effects of CBT

and STPP will be assessed with a scale developed and used in the ADAPT study. Serious adverse effects will be reported through the usual procedures.

Duration of treatment
SCC will consist of 12 sessions delivered over 16 weeks, CBT 20 sessions over 24 weeks and STPP 30 sessions over 30 weeks. Response to treatment will be reviewed at 6, 12, 28, 52 and 86 weeks by the research assessor.

Withdrawal from study treatments
Subjects will be withdrawn from the trial and appropriate treatments given if (a) they or their parents want to withdraw, (b) they experience serious adverse effects from treatment (specified in the manual) that persist after reduction or modification of treatment, or (c) they have severe symptoms (specified in the manual; e.g. serious suicidal attempts) *and* are judged either to be getting worse or not to have improved on the Clinical Global Improvement Scale (CGI) at week 6 or week 12. Reasons for withdrawal from the trial and definitions of adverse effects would be reviewed at the conference calls. All withdrawals will be followed up (see **3.8**).

Logistics within each centre
The child psychiatrist and therapists will be part of the multidisciplinary teams within the clinics and accept weekly referrals and give the interventions on site. The child psychiatrist will deal with other issues, such as emergencies, in consultation with the consultant psychiatrist in the clinic.

Planned inclusion and exclusion criteria

Which entry criteria?
This trial is concerned with the relative *effectiveness* of three interventions. It is not a test of efficacy, as the efficacy of both CBT and to some degree STPP has been examined in previous studies (see above). Therefore, we shall employ relatively few entry criteria, as we wish to test the interventions in a diverse sample that is likely to be representative of the kinds of cases that NHS clinicians would take on for treatment. Many previous trials with this population have limited generalisability because of the substantial proportion of patients presenting who were excluded on grounds correlated with symptom severity (e.g. suicidality) or socioeconomic status.

Inclusion criteria.
(1) age 11 through 17 years. (2) current DSM-IV MD

Exclusion criteria.
(1) Generalized learning problems (clinical diagnosis) or a pervasive developmental disorder that results in an inability to compete the questionnaires, or both, (2) pregnant, or currently having sexual relations without reliable contraception, (3) currently taking another medication that may interact with an SSRI and unable to stop this medication [uncommon] .

Psychosocial assessments and outcome measures (see the figure at the end of this annex)

Principles of measurement
The measures will be made across multiple domains (depression specific, quality of life, user satisfaction, comorbid problems, economic costs), using multiple methods (interviews, questionnaires, records), and multiple sources (adolescent, parent, teachers). This strategy should maximize the clinical validity of the outcome assessments. It will also help to minimize bias arising

from any single source of information. Wherever possible, these measures will be made by individuals who are unaware of treatment allocation.

Precautions to ensure that the outcome assessors are unaware of treatment allocation and to minimize biases that could arise from knowledge of treatment allocation

Potential biases arising from knowledge of treatment allocation will be minimized using the following strategies. First, the main outcomes will be collected by an outcome assessor (OA), who will be unaware of treatment allocation. Thus, the patient and parents will be asked before the interview with the OA not to reveal anything about treatment. The OA and the therapist/s will not share the same room. Second, the OA will be asked at the end of the study to guess which treatment was given, so that the effects of possible bias can be examined in the analysis. Third, all the OAs' interviews will be audiotaped and a random sample re-rated by an assessor who has no knowledge of treatment allocation. Fourth, where possible outcome information will be collected from sources that are unlikely to know what treatment the child has had. For instance, school attendance and performance (both of which are included in HoNOSCA) will be collected from the school. Fifth, the patient and parent's expectancies of treatments would be assessed at the start of the study using an expectancy scale (Wood et al., 1996).

Initial clinical assessment (2 weeks before the first research assessment)

The first assessment of eligibility for the trial would be conducted by the study child psychiatrist, who would complete the depression section of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), the Moods and Feelings Questionnaire (MFQ) and the Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA).

Achieving and maintaining reliable assessments by the outcome assessors

The reliability and validity of all the outcome measures have been tested in previous studies (Goodyer et al., 2007; Wood et al., 1996) or in other research projects with depressed adolescents, or both. All measures would be completed by the OAs at the four research assessments, and if the subject withdraws from the study. The OAs in the two sites would be trained on the same training course and audiotape reliability of the interview-based measures would be tested before and during the study both within and between sites. The assessors will be expected to achieve audiotape reliability against 'gold standard' tapes of HoNOSCA and K-SADS interviews of kappa >.75 by the 3rd month of the study and to maintain a similar level of reliability during the study (to prevent rater drift).

Primary outcome. The primary outcome measure will be persistence of symptoms at 52 weeks and recurrence of symptoms by 86 weeks. These will be recorded using a parent and self report measure, the Moods and Feelings Questionnaire (MFQ)(Daviss et al., 2006). This instrument has good criterion validity and sensitivity to change. Other factors such as school performance and peer relationships must also be encompassed.

Secondary outcomes The Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA) will be completed (Gowers, Levine, Bailey-Rogers, Shore, & Burhouse, 2002). This instrument measures the outcomes of child and adolescent psychiatric disorders across a range of areas relevant to the *quality* of the child and family's life, including psychiatric symptoms, peer relationships, family functioning and school functioning. HoNOSCA is widely used in the NHS. Indeed, it was used by the Audit Commission in its recent survey of all child mental health services in England. It is of known reliability, sensitive to change, and correlates well with the clinician's judgement of outcome(Gowers et al., 2002). The HoNOSCA will be completed by the OA with information collected from the adolescent, the parent and the school.

The adolescent and parent will be interviewed separately using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)(Kaufman, Birmaher, Brent, Ryan, & Rao, 2000). This covers most DSM disorders and has good psychometric properties. Parent and child data would be combined into a best-estimate. Data from the K-SADS would be used to generate a categorical measure of time to remission using predetermined criteria. In addition, depressive symptoms would be assessed with the Children's Depression Rating Scale (CDRS)(Poznanski, Freman, & Mokros, 1985), a paediatric version of the Hamilton scale. Both the K-SADS and the CDRS have been widely used in previous studies of adolescent depression, so we can make direct comparisons with those studies. The K-SADS also measures disorders that are comorbid with MD, including anxiety and behavioural disorders. In addition, the version we shall use includes a) a continuous measure of global functioning, the Children's Global Assessment Scale (Shaffer, Gould, Brasic, & al., 1983) (CGAS) and b) an ordinal measure of improvement, the Clinical Global Improvement Scale (CGI). Global self-report measures of satisfaction with treatment (Wood et al., 1996) would be completed by the child and parent. The Mood and Feelings Questionnaire (Daviss et al., 2006) would be completed every month during the treatment phase by the child and at each assessment thereafter by the child.

Non depressive psychological predictors of outcomes There are four potentially key components that may influence treatment response that need to be incorporated in this study. First, a recent meta-analysis concluded that **personality disorders** are associated with poorer outcomes in treatment studies of adult depression(Newton-Howes, Tyrer, & Johnson, 2006). As far as we are aware personality disorders have not previously been examined as predictors of treatment outcome for depression in adolescence, nor assessed as secondary outcomes. However there is a strong case for both, because personality disorder symptoms in adolescence are associated with subsequent depression in adolescence (Daley, Rizzo, & Gunderson, 2006)and adult life (Johnson et al., 1999). Self-report and interview measures of personality disorder symptoms have been used previously with adolescents. Second, **suicidal behaviour** is a key negative outcome of depression during adolescence (Fombonne et al., 2001). Reducing the risk for suicidal behaviours is a priority in treating adolescent depression. A key risk factor identified from prior studies is the presence of a behavioural style of impulsive aggression (Brent et al., 2002) that may adversely influence treatment response. Third, **individual differences in the quality of therapeutic relationship** have been shown to influence treatment response in studies of psychological therapies with adolescents (Shirk & Karver, 2003). Very little is known about influences on the quality of therapeutic relationship and this study provides an opportunity to find out whether type of treatment is a factor, and in turn whether this is associated with treatment outcome. We will measure personality disorder symptoms at baseline and at 52 and 86 weeks follow up, using a brief screening measure (Langbehn et al., 1999)and the antisocial and borderline personality disorder sections of the SCID – II (First, Spitzer, Gibbon, & Williams, 1997). Impulsive aggression at baseline, 52 and 86 weeks follow up will be assessed with a questionnaire measure used in previous studies of adolescent suicidal behaviours (Brent et al., 2002). Quality of the treatment relationship will be assessed at 6, 12 and 36 weeks using a 12 item self report measure of the adolescent's perception of the working alliance (Horvath & Luborsky, 1993). Fourthly, **mood-related ruminative response style** (MRRS, repetitive thinking about symptoms when feeling sad) increases risk of persistence of depression (Goodyer et al, 2003); in addition, cognitive-behavioural therapy reduces rumination more than treatment as usual in depressed adolescents (Wilkinson and Goodyer, 2008). We predict that in depressed adolescents with high MRRS, this high MRRS is likely to be a key perpetuating factor in the depression. They are likely to have a greater benefit from CBT (compared with other treatments) than patients with lower MRRS. We therefore predict a treatment group x MRRS interaction: the advantage of CBT over treatment as usual will be greater in adolescents with high baseline MRRS. We also hypothesise a greater fall in MRRS in

adolescents allocated to CBT than STPP than SSCC. It is also possible that improved MRRS precedes, and mediates, the improved depressive symptoms in psychological treatments as opposed to SSCC (Wilkinson and Goodyer, 2008), therefore it is important to measure MRRS at all time points. Mood-related response style will be measured at all time points using the self-report Responses to Depression Questionnaire, a modified version of the Response Styles Questionnaire (Nolen-Hoeksema and Morrow 1991), with wording altered to make it more appropriate for adolescents. A small study suggested that CBT leads to greater reduction in self-devaluation (as measured by the Depressed States Checklist, DSC) than SSCC in depressed adolescents (Wilkinson 2007). Low self-devaluation (measured by the DSC, Teasdale and Cox 2001) increases the chance of recovery from depression in adolescents (Park et al 2005), demonstrating the importance of reducing this cognitive style. As with MRRS, we predict a treatment group x self-devaluation interaction: the advantage of CBT over treatment as usual will be greater in adolescents with high baseline self-devaluation. We also hypothesise a greater fall in self-devaluation in adolescents allocated to CBT than STPP than SSCC. We shall measure self-devaluation, using the DSC, at baseline, 36 weeks and 86 weeks.

*Genes and Hormones***.** Genetic polymorphisms have demonstrated differential response to both antidepressants and talking therapies in some studies. (Smits, Smits et al. 2004; McMahon, Buervenich et al. 2006; Kotte, McQuaid et al. 2007). Genome-wide association studies looking for common genes of small effect have demonstrated few polymorphisms that are reliably found more in people with a history of depression than controls. A newer approach for heterogenous disorders such as depression is to look for rare genes of large effect. While these would only be found in a small number of participants, the large odds ratios will lead to greater statistical power. Such polymorphisms would reveal useful information about the biology of the disorder. Such an approach has had success in phenotypes such as obesity.

We plan to test for rare and common polymorphisms on up to 200 genes thought to be relevant to depression. We shall use our genetic information to test for genetic polymorphisms relevant to the following contrasts:

1. Comparing depressed cases from our study against controls (from the WTCCC control bank) for genetic polymorphisms influencing risk of depression
2. Genetic polymorphisms predicting persistence of depression
3. Genetic polymorphisms predicting preferential response to specific therapies

In addition, we have another sample of adults with recurrent undergoing a different randomized trial of psychological therapy (Prevent, PI=Willem Kuyken, University of Exeter). This study has ethics approval for genetic testing. We shall use this sample to try to replicate genetics results from IMPACT.

Genetic statistical analysis will be done in partnership with the lab of our expert genetics collaborator, Prof Sadaf Farooqi, Institute of Metabolic Sciences, University of Cambridge. Genotyping will be done by a commercial company, AROS Inc, based in Denmark. AROS are GLP accredited for work on human DNA samples and have been used by multiple research groups, including by the University of Cambridge in Cambridgeshire LREC-approved studies.

High levels of the stress hormone cortisol are associated with depressive episodes lasting longer (Herbert, Goodyer et al. 2006). We predict that high cortisol predicts greater response to CBT than STPP than SCC. We predict that high cortisol predicts higher levels of depressive symptoms at

future follow-up points. We predict that there will be greater falls in cortisol in participants that are allocated to cognitive-behavioural therapy and psychodynamic therapy than in those allocated to treatment as usual; and that lower cortisol at 26 weeks will be associated with reduced risk of relapse up to 86 weeks.

At baseline, participants will be asked to collect saliva samples at waking, 30 minutes after waking and 22.00hrs for two consecutive days, for cortisol assay. There is excellent correlation between plasma and salivary levels of cortisol. Samples will be averaged across the two days to reduce the effects of day-day variation. Saliva will again be collected for cortisol assay at waking, 30 minutes after waking and 22.00hrs for two consecutive days at the 36 week assessment. One sample of saliva will be collected in the Oragene system for DNA extraction and triallelic 5-HTTLPR and 5-HT2A rs7997012 genotyping. Saliva for genetic testing will take place at one of the research assessments, ideally the baseline assessment. Saliva collection kits will be given to participants at the baseline and 36 week assessments, with instructions on how to collect these and post them to Cambridge. Samples will be posted to Cambridge then frozen until analysis. All biological analysis will take place in collaborator laboratories in Cambridge. Saliva collection for this part of the study will be totally optional: it will be made clear to participants that they will be able to take part in the treatment study and not provide saliva for gene/hormone testing without this affecting their care nor their participation in the treatment study. Participants would be offered £10 for providing saliva for genetic analysis, £10 for providing saliva for baseline cortisol assay and £10 for providing saliva for 36 week cortisol assay

Assessments by therapists

The therapists would complete the CGI and the HoNOSCA every 6 weeks from the beginning to the end of treatment. Although these ratings are not 'blind', they will help us to measure speed of response.

Economic evaluation

Health economic analysis would be conducted by the Centre for the Economics of Mental Health at the Institute of Psychiatry, London. The primary objective is to evaluate the relative costs and cost-effectiveness of the three treatments. Major depression is an important and costly problem among adolescents yet evidence to support the provision of cost-effective treatments is lacking (Romeo, Byford, & Knapp, 2005). Since STPP and CBT are both more resource intensive than best practice SCC, their provision requires additional health service resources that could be used elsewhere. In order to ensure such resource allocation is cost-effective, it is necessary to demonstrate that the additional resources spent can be justified, either in terms of savings as a result of reduced demand for other services, or in terms of gains in effectiveness.

Data collection

The economic evaluation will take a broad societal perspective, including use of all hospital and community health and social care services (public, private or voluntary sectors) and the cost of schooling and education sector support services. Family costs in the form of travel to trial intervention sessions and productivity losses of the primary carer resulting from their child's illness will also be recorded. Economic information will be collected in interview at baseline and all follow-up points using the Child and Adolescent Service Use Schedule (CA-SUS), developed by the applicants in previous research in child and adolescent mental health populations and

adapted for the purpose of the study (Barrett, Byford, Chitsabesan, Kenning, & Harrington, 2006; Byford et al., 1999; R. Harrington et al., 2000). Data on the trial interventions, STPP and CBT, will be collected from clinical records to avoid patients revealing their treatment group to the research assessors.

The cost of the trial interventions will be calculated using a micro (or bottom-up) costing approach (Drummond, O'Brien, & Stoddart 2005)which will involve estimation of indirect time spent on individual cases, including supervision, as well as detailed recording of direct face-to-face contact. Unit costs will be calculated using data on salaries, employer on-costs (National Insurance and superannuation), conditions of service and appropriate administrative, managerial and capital overheads (Curtis & Netten 2004). The unit costs of all other resources used by trial participants will be estimated, where possible, on the basis of information provided by local service providers. For some services, particularly those which add little to the total cost of care, national published unit cost data will be employed. Productivity losses will be calculated using the human capital approach, which involves multiplying days off work due to illness (in this case illness of the young person) by the individual's salary. The human capital approach has been criticised for its inability to consider labour market responses to time off work due to illness, such as colleagues covering for an absent individual, the individuals ability to catch up on work missed on their return and the ability to replace workers from the pool of unemployed (Koopmanschap & Rutten, 1996). Thus, the human capital approach will tend to overestimate the true cost of productivity losses. To take this into SCCount, the impact of productivity losses will be explored in sensitivity analysis.

Perspective of the analysis

The perspective of the economic component of the trial will be societal (Johannesson, 1995). Costs will, however, be disaggregated to enable each sector in society to evaluate the impact of the treatment alternatives from their own perspective.

Analysis of costs

Analyses will be carried out on an intention-to-treat basis using a statistical analysis plan drawn up prior to data analysis. Although cost data are often found to have a non-normal distribution, analyses will compare mean costs using standard parametric t-tests with the validity of results confirmed using bootstrapping (Efron & Tibshirani, 1993). The advantage of this approach, as opposed to logarithmic transformation or non-parametric tests, is the ability to make inferences about the arithmetic mean (Barber & Thompson, 1998). The primary cost analysis will explore differences in total costs over the period from baseline to final follow-up (18 months after randomisation). Multiple regression will be used to adjust for the following pre-specified baseline characteristics: severity of illness, age, gender, comorbid behavioural and anxiety disorder, centre and baseline costs. The impact of drop-out will be assessed by comparing baseline characteristics of patients with and without full economic data. Subgroup analyses by severity of illness and centre will be performed using tests of interaction. To test the generalisability and robustness of the results, extensive sensitivity analyses will be carried out (Drummond et al., 2005). Threshold analysis will be used to determine the value of key cost components at which the results of the analysis will change and unit costs or resource-use components which are based on certain assumptions will be tested to determine the effect of variation in the assumptions made.

Analysis of cost-effectiveness

Cost-effectiveness analyses will be undertaken using the primary clinical outcome, the MFQ Additionally, a cost-utility analysis will be carried out using the EQ-5D measure of health-related quality of life (Brooks, 1996)which is a generic scale capable of generating quality adjusted life years (QALYs). This will enable broader comparisons with studies employing the same measure and direct

comparison with willingness to pay (for an additional QALY) norms. Cost-effectiveness will initially be explored through the calculation of incremental cost-effectiveness ratios (ICER) (the difference in mean costs divided by difference in mean effects) (Van Hout, Al, G.S., & Rutten, 1994). Repeat re-sampling from the costs and effectiveness data will then be employed to generate a distribution of mean costs and effects for the two treatments (Efron & Tibshirani, 1993), which can be used to calculate the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for a unit improvement in outcome. Cost-effectiveness acceptability curves will be presented by plotting these probabilities for a range of possible values of the ceiling ratio (Fenwick , Claxton, & Sculpher, 2001). These curves incorporate the uncertainty that exists around the estimates of mean costs and effects as a result of sampling variation and uncertainty regarding the ceiling ratio.

Sensitivity analysis

To test the generalisability and robustness of the results, extensive sensitivity analyses will be carried out (Eisenberg, 1989). Threshold analysis will be used to determine the value of key cost components at which the results of the analysis will change and unit costs or resource-use components which are based on certain assumptions will be tested to determine the effect of variation in the assumptions made.

Predicting costs from baseline characteristics

To determine useful predictors of service utilisation and cost, multiple regression analysis will be used to examine the relationships between the total cost of care packages and client characteristics at baseline, including age, gender, ethnicity, diagnosis, comorbidity, severity of illness, level of education, family social class.

Arrangements for follow-up

Follow-up assessments will be conducted at 6, 12, and 36, 52 and 86 weeks after the start of treatment. Subjects who withdraw from the trial will be assessed both at the point of withdrawal and at the regular assessment points. We recognize that in adults there is some evidence that CBT may lead to medium-term beneficial effects (Scott et al., 2000). There is also a strong theoretical and empirical proposition that STPP may have sleeper effects that will emerge later than those of SCC or CBT (Bateman & Fonagy, 2001; Kolvin, Garside, Nicol, Wolstenholme, & Leitch, 1981; Kolvin, MacMillan, & Wrate, 1988). Therefore we have included arrangements for medium-term follow-up because the key question in the HTA brief is what works to reduce persistence and recurrence, both of which can only be determined with comprehensive assessments at 52 and 86 weeks after treatment begins.

Randomization

Remote telephone randomisation: Christie Hospital, Manchester

The research child psychiatrist will complete a brief demographic and clinical checklist, confirm eligibility and obtain consent. The checklist will then be faxed/phoned/emailed to the randomization centre, the Department of Medical Statistics at Christie Hospital, Manchester. Allocation will be by minimisation controlling for severity, treatment centre, sex, comorbid behavioural and anxiety disorder, and age. The case will then be assigned a study number and treatment allocation will be faxed/phoned/emailed to the appropriate to the research child psychiatrist.

Why stratify by severity and comorbidity ?

A large number of factors could influence treatment response but severity is one of the most robust (I.M. Goodyer et al., 2007; R. Harrington, Kerfoot et al., 1998; R. C. Harrington & Clark, 1998).

Severity is usually conceptualized in child psychiatry as the mixture of symptoms and impairment. We shall therefore assess severity using the CGAS (Shaffer et al., 1983), which is a widely-used measure of symptoms and personal impairment. A CGAS score of 40 will be used as the cut-off because in previous research that point has been at around the median of severity (I.M. Goodyer et al., 2007 ; Wood et al., 1996) and because it has intrinsic clinical validity in a study of depressed adolescents (scores of 40 or less indicate significant impairment in 2 or more areas of life, and unable to function in one of these areas and/or at least one serious suicidal attempt). Comorbidity will be assessed by the child psychiatrist using the K-SADS (Kaufman et al., 2000) when disruptive behavioural disorders and anxiety disorders will be assessed and used as 2 categories for randomisation purposes.

Justification for sample size and statistical power (see the figure at the end of the annex)

Projected recruitment rate

We will repeat the strategy that we used successfully in previous trials, recruiting from 18 routine CAMHS clinics, 6 each within 3 health regions (North West England, East Anglia and North London). In North West England the clinics will be The Wirral, Liverpool, Salford, Bolton, North Manchester, South Manchester, and Bury (total population 2.6 million). In East Anglia these clinics will be Cambridge, Peterborough, Huntingdon, Norwich, Bury St Edmunds and Ipswich (total population 2.5 million). We have shown in previous studies that we can recruit around 40-50 cases per year from each clinic (I.M. Goodyer et al., 2007 ; R. C. Harrington & Clark, 1998). Over the 18 month recruitment phase we should identify about 810 potential cases (45 cases per clinic) in total. However, we expect 25% to refuse the trial (these estimates are based on our previous RCTs) . So, we expect to identify 607 cases in scope for the trial. Each trial site has some experience of participating in randomised controlled trials and accumulated experience in recruiting and consenting patients for psychosocial treatment trials. The trial leadership includes clinicians in senior positions at the participating centres, further increasing the chance of embedding the trial in the routine provision of services. The presence of a clinical coordinator part-time at each of the sites will further ensure optimal recruitment and retention in the trial as well as adherence to the SCC protocol.

Projected success of follow-up

In previous trials with depressed or suicidal adolescents we obtained primary outcome data on >95% of randomised cases (I.M. Goodyer et al., ; R. Harrington, Kerfoot et al., 1998; R. C. Harrington & Clark, 1998; Wood et al., 1996). In the present proposal we shall assume 10% non-compliance at the post-treatment (52 wks) assessment. This means that in intent-to-treat analysis at the 52 weeks point we should have 180 cases in each group. Compliance with the final assessment should also be good, being 91% and 92% after six months in our previous trials (I.M. Goodyer et al., 2007; Wood et al., 1996) .

Evidence of the feasibility of this recruitment and follow-up strategy

The ADAPT study showed that the strategy is feasible using 6 CAMHS clinics in Manchester and Cambridge. In this RCT 208 patients were randomised and 202 completed primary endpoint analysis (I.M. Goodyer et al., 2007).

Statistical power of the intent to treat analysis for the primary outcome

The brief asks for comparisons to be made between CBT, STPP and SCC. In trials involving more than two treatments, there are a number of comparison that may be made between treatment

groups. We propose to make two (i) the two specialist treatments CBT & STPP will be compared (ii) the specialist treatments will be compared with SCC entailing. A 2.5% two-tailed significance level has therefore been used in the power calculation.

Statistical power to detect a difference between treatments

The hypothesis of comparison may be either of superiority, equivalence or non-inferiority, and these might differ SCCording to the comparison. For example a superiority design might be used for the comparison of the specialist treatments, while a non-inferiority design might be used for the comparison of the specialist treatments with SCC. There is conflicting evidence regarding which of these is the most relevant comparison. For example the ADAPT study (Goodyer et al., 2007), a superiority trial, suggested no difference between SSRI + SCC as compared to SSRI + CBT. Power has been estimated for each of the three designs. Confidence intervals regarding the treatment effects may therefore be more important than statistical hypothesis tests in the interpretation of the trial outcome data.

Therapist influence on sample size

The trial will compare therapist-delivered treatments. In order that it has generalisability it has been suggested that statistical models of outcome estimate between-therapist variations (Roberts, 1999) . Variation in outcome between health professionals has study size implications in terms of both patients and therapists (C. Roberts, 1999), (Lee & Thompson, 2005). Analysis of data from the ADAPT study gave an estimate of the intra-therapist correlation coefficient after adjustment for baseline covariates of zero at 28 weeks, but it is acknowledged that intra-therapist variances were imprecisely estimated due the sample size in terms of patients and therapists . Sample size and power estimation therefore considered an intra-therapist correlation coefficient of 0.025 and 0.05. Sample size calculation is based on a summary level statistical analysis taking the approach described by Roberts & Roberts (Roberts & Roberts, 2005).

Sample size and Power

It is proposed that the proposed design of the trial will run in 6 CAMH clinics in each of three centres, giving 18 clinics with a minimum of one therapist for each treatment modality in each clinic and 10 patients per treatment modality recruited in each clinic. This gives a total sample size of 540. The ADAPT trial gave an SD of 14.6 at 28 weeks follow-up and correlation between baseline and follow-up of 0.41 for MFQ, proposed primary outcome of this study. We have assumed 5 points on the MFQ to be the minimum clinically important difference. This is approximately 25% of the change in the MFQ scale from baseline to 28 weeks. It is equivalent to a 1 point improvement on 5 of the 34 items of the scale. It is a standardize effect size of 0.34 (small to medium) and corresponds to non-overlap between treatments of approximately 25% (Cohen, 1988). The table below gives estimates of power for Superiority, Non-Inferiority and Equivalence designs for an intra-therapist correlation coefficient of 0.0, 0.025 or 0.05. Provided that the intra-cluster correlation is less than 0.025 a superiority analysis comparing CT with PP will have a power of over 80%. By virtue of the increased sample size specialist comparisons of the specialist treatments (CBT & PP) with treatment as usual (SCC) will have substantial power. These power calculations assume a cross-sectional analysis, but statistical analysis will be based on longitudinal data using a linear mixed model (details below) use of such a model will increase the power of the statistical analysis as data is in effect shared across follow-up time-points.

Table. Power assuming 18 therapists for each treatment modality, and 10 patients per therapist

		Design	
Intra-therapist correlation	Superiority	Inferiority	Equivalence
CBT vs PP			

0	88%	93%	87%
0.025	80%	88%	75%
0.05	73%	82%	64%
(CBT+PP) vs SCC			
0	96%	98%	96%
0.025	91%	95%	90%
0.05	85%	91%	82%

ADAPT had 92% follow-up at 28 weeks.

Statistical analysis of Clinical Outcome Measure

Analysis will be undertaken independently of the study centres by the Biostatistics Group at the University of Manchester under the supervision of the trial statistician, Chris Roberts. All analyses will be SCCording to the 'intention to treat' principal. A sub-group analysis by severity will also be conducted using a treatment-severity interaction term. Characteristics of the treatment groups will be described at baseline. Whilst great effort will be made to minimize missing data, preliminary analysis will compare the characteristics of subject with and without complete data. The statistical analysis of the primary outcome measure (MFQ) and the secondary measures will be estimate the treatment effect using a longitudinal linear mixed effects statistical models adjusting for pre-specified prognostic variables (baseline severity, treatment centre, comorbid behavioural and anxiety disorders, sex, and age) and time point of assessment. The model will include subject level random intercept and gradient effects and also random effects for therapist. Where outcome measures have non-normal residuals either an appropriate transformation will be used to normalize data. Ordered categorical secondary outcome measures such as the CGI scales and suicidality rating scales will be analysed using the proportional odds model (McCullagh, 1980). No interim analyses of outcome will be carried out unless requested by the trial data monitoring and ethics committee. A sub-group analysis by severity will also be conducted using a treatment-severity interaction term.

Statistical power for the health economic analyses

Results from the ADAPT study do not support the hypothesis that the additional cost of specialized interventions for adolescents with depression are recouped by savings elsewhere (mean cost CBT+SSRI+SCC £6940 versus SSRI+SCC £4640; p=0.059). Two high cost individuals in the CBT arm, who had spent the majority of their time in the trial in hospital, greatly influenced these results. However, even when these outliers were removed, the CBT group remained more expensive (£5531 versus £4640; p=0.202). We therefore hypothesise that the specialist arms of the trial will be more expensive than SCC. The cost of the three treatment interventions in the current study are estimated to be £300 for SCC (ten 30-minute sessions), £1200 for CBT (twenty 60-minute sessions) and STPP £2400 (forty 60-minute sessions). Adding these costs to the cost of SCC in the ADAPT study gives estimated total costs per patient of £4678 for SCC, £5578 for CBT and £6778 for STPP. A 3-arm one-way analysis of variance calculation for sample sizes, using a common standard deviation derived from the ADAPT study, suggests a sample size of 163 per arm would be adequate to detect differences between the three groups as significant, with p=0.05 and 80% power (or 84% power with a sample size of 180 per arm). A contrast analysis of specialised treatments compared to SCC suggests 81% power at the p=0.05 level of significance and 72% power at the p=0.025 level of significance with a sample of 180 per arm.

It is possible that the ADAPT study, with only a 28-week follow-up, was not long enough to pick up changes that specialist therapies may have in the medium to long-term. This may be particularly true of STPP which is a longer intervention than CBT or SCC. Thus, it could be hypothesized that the additional cost of the specialist treatments would be recouped by reductions in the use of services over the longer-term. However, there is currently no evidence to support or dispute this hypothesis so it would be inappropriate to make this assumption for sample size calculations. The proposed study will help to clarify this.

Trial management

Management committees and procedures

A steering committee will be chaired by a nominee of the host institution, Cambridge University and will include the applicants, representatives of user groups from the three sites, an external trials expert (Professor David Brent from Pittsburgh University), and representatives from the 3 lead NHS Trusts. It will meet twice a year. A trial management committee will comprise the applicants, the research workers and the administrators/secretaries. It will meet every 2 months. Day-to-day management of the trial will be undertaken by the principal investigators and an administrator/secretary at each site. Data entry will take place at each site, with appropriate quality control procedures (eg, double entry, manual checking). There will be regular conference calls between the therapists, and between the outcome assessors, concerning issues such as what constitutes side effects and what constitutes a satisfactory response. Clinical decisions for each child will be discussed at this biweekly conference process (shown to be feasible in the NIMH Multimodal treatment study of attention deficit disorder). This should minimize differences between centres in the conduct of the trial. In addition a data monitoring committee will be established SCCording to the guideline set out in the DAMOCLES Charter (DAMOCLES, 2005)which will include an independent expert in the field and an experienced trial statistician.

User involvement

All three sites involved in the program have effective and well functioning user groups involved in both service and research design. The present proposal has already had the benefit of user consultation. When approved, the protocol will be taken to the user groups of the participating Trusts and recruitment and consenting strategies will be elaborated together with both adolescents and carers. The study will aim to maintain user involvement throughout the trial through a partnership arrangement with the relevant user groups in the hope that (a) aspects of the protocol that might generate unnecessary burden, discomfort or adverse reactions in young people or their carers will be identified early and their effect moderated, (b) that the experience of the trial for participating young people will be elaborated, appropriate explanations of study procedures generated, where necessary protocols modified with the aim of minimizing attrition from the assessment protocol, (c) ambiguities in emerging findings can be helpfully elaborated by both carers and young people particularly in relation to cultural and other BME issues. The user representatives (paid for their time) will be charged with communicating with respective user groups to feed back on issues of relevance to the trial.

Anticipating problems

The rate of recruitment will be kept under bimonthly review by the trial management committee. Divergence from target rates of randomization (see section **4**) will trigger review of recruitment in each district and the possible addition of other district services. Divergence of target rates of follow-up will trigger review of follow-up procedures. The applicants are experienced in recruiting large samples into non-commercially funded trials and following them up. Before inclusion in the study, all participating young people will need to give written informed consent after full and adequate

written and oral information about the nature, purpose, possible risks and benefits of the study. It is particularly important that young people appreciate the efforts at maintaining confidentiality, complying with data protection regulations, the treatment of audio tapes, the independence of assessors from treatment staff, the maintenance of anonymity etc. Young people are likely to be particularly sensitive about these issues. Full disclosure is considered essential.

Trial support facilities

The trial is submitted for adoption to the Mental Health Research Network. They will provide active support to ensure the required rate of recruitment and longitudinal assessment over the duration of the trial. The trial is being supported by 5 Universities, Cambridge, UEA, University College London, Kings College London, Manchester, and the 5 NHS Trusts [Cambridge and Peterborough, Norfolk Mental Health, Manchester Children's, Cheshire and Wirral, Central and North West London] who will sponsor the study.

Quality assurance monitoring

In addition to monitoring the adherence to the three treatment manuals carried out by the applicants, independent quality assurance will be undertaken in relation to the collection of data quality at each site. Each centre will be visited by a peer group selected from the other centres at least twice a year to ensure full compliance with the protocol. The visiting team will report to the coordinating committee of the study and all reports will be regularly discussed to ensure continuous quality monitoring.

Dissemination

The results of the research will be targeted for publication in peer-reviewed journals of general and special interest. Reporting will conform to the CONSORT guidelines. The applicants are experienced in publishing in peer-reviewed journals. The results will also be reported at national meetings and at a national workshop to develop evidence-based practice parameters.

4. PROJECT MILESTONES

Months	Tasks	Randomized, n	52 wk assess., n
1-3	Staff training, construction of databases, initial reliability assessments. Mo. 3 - check outcome assessors are rating reliably (see **3.6.4**) and therapists are competent in all therapies (see **3.4.2**)		
4-6	Mo. 5 – 2nd check on inter and intra site reliability of outcome assessments. 2nd formal check of competence of therapies.		
7-9	Mo. 7 - first steering committee reviews progress and need to recruit other districts; Mo. 9 3rd formal check of competence of therapies	108	
10-12	First check of data fidelity on data base	216	
13-15	Mo. 13 - 2nd decision point about need to recruit other districts; mo. 15 4th formal check on competence of therapies	324	
16-18	Mo. 16 – 3rd check on inter and intra site reliability of outcome assessments	432	
19-21	Mo. 20 - final decision point about need to recruit other clinics	540	108
22-24	Second check of data fidelity on data base	600 recruited	216
25-27	Mo. 25 - 5th formal check on competence of therapies		324
28-30	Mo. 15 – 4th check on inter and intra site reliability of outcome assessments		432
31-33			540
34-36	Confirm all primary endpoint assessments complete		600
37-40	Confirm all 28 week assessments complete. Check all data for primary endpoint analysis entered, clean and ready for analysis		
41-42	Enter 28wk data. Data analysis, write report		
52-56	86 week assessments will be completed		

EXPERTISE

Ian Goodyer has a long-standing interest in adolescent depression and has much experience in recruiting large samples of depressed young people for his longitudinal studies. He was a principal investigator in the HTA funded ADAPT RCT. He runs a special clinic for depressed youngsters. He will jointly provide the East Anglia site and expertise on measurement of outcomes and input into the SCC manual and co-ordinate data for the East Anglian site. **Peter Fonagy** has a long standing interest in psychodynamic psychotherapy, has published extensively on effectiveness of brief therapy in children and has co-ordinated randomised controlled trials in young people. He will provide expertise on design, measurement, STPP manual and co-ordinate data compilation for the North London site. **Sarah Byford** will supply expertise in economic evaluation. Sarah worked on the ADAPT study and on the Manchester treatment trial (Byford et al., 2007; Byford et al., 1999). Sarah has a particular expertise in assessing the costs and cost effectiveness of child psychiatric disorders. **Jonathan Hill** is an expert in mental health and personality assessment in adolescents and has published extensively on adolescent development and depression. He will co-ordinate assessment and measurement data over the trial and oversee data compilation in the North West site. **Bernadka Dubicka** was the clinical trial co-ordinator in the ADAPT study and will co-ordinate recruitment in the North West of England, assist in compiling the SCC manual and rate a random selection of the audiotapes for adherence to the manual. **Chris Roberts**, of the Biostatistics Group at the University of Manchester, will supply expertise in study design, randomization, and data analysis. **Chrissie Verduyn** and **Shirley Roberts** will provide expertise in the CBT interventions and will rate a random selection of the audiotapes for adherence to the manual. **Mary Target** has expertise in clinical and research processes associated with brief psychodynamic psychotherapy in young people and will supervise STPP interventions and rate a random selection of the audiotapes for adherence to the manual. **Rob Senior** has expertise in clinical research with children and adolescents. He will co-ordinate clinical recruitment in the North London site, supervise active clinical care [SCC], contribute to the SCC manual and rate a random selection of the audiotapes for adherence to the manual. **Raph Kelvin** has expertise in adolescent depression research, co-ordinated the recruitment and management of patients in the Cambridge arm of the ADAPT study and directs the mood disorders clinic in Cambridge. He will contribute to the SCC manual, supervise SCC in the East Anglian arm and rate a random selection of the audiotapes for adherence to the manual

5.1 Supervision of junior staff (therapists and outcome assessors -- see sections 3.4.2 & 3.6.4)

Supervision of staff will be provided in each centre. The principal investigators will meet weekly with the research staff to monitor study progress, check reliability and supervise data entry.

REFERENCES

Apter, A., Bernhout, E., & Tyano, S. (1984). Severe obsessive compulsive disorder in adolescence: a report of eight cases. *J Adolesc, 7*(4), 349-358.

Asarnow, J. R., Jaycox, L. H., Duan, N., LaBorde, A. P., Rea, M. M., Murray, P., et al. (2005). Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics: a randomized controlled trial. *Jama, 293*(3), 311-319.

Barber, J. A., ., & Thompson, S. G. (1998). Analysis and interpretation of cost data in randomised control trials: review of published studies. *British Medical Journal, 317*, 1195-2000.

Barrett, B., Byford, S., Chitsabesan, P., Kenning, C., & Harrington, R. (2006). National study of mental health provision for young offenders. Part II: service use and cost. *British Journal of Psychiatry (in press)*.

Baruch, G., Fearon, P., & Gerber, A. (1998). Evaluating the outcome of a community-based psychoanalytic psychotherapy service for young people: one year repeated follow-up. In D. R & P. M. (Eds.), *Rethinking Clinical Audit* (pp. 157-182). London: Routledge.

Bateman, A. W., & Fonagy, P. (2001). Treatment of borderline personality disorder with psychoanalytically oriented partial
hospitalization: an 18-month follow-up. *American Journal of Psychiatry, 158*, 36-42.

Beedell, C., & Payne, S. (1987). *Making the Case for Child psychotherapy: A Survey of the Membership and Activity of the Association of
Child Psychotherapists:* . Bristol.: School of Applied Social Studies, University of
Bristol.

Boston, M., & Lush, D. (1994). Further considerations of methodology for evaluating psychoanalytic psychotherapy with children: Reflections in the light of research experience. *Journal of Child Psychotherapy, 20*, 225-229.

Brent, D. A., Holder, D., Kolko, D., Birmaher, B., Baugher, M., Roth, C., et al. (1997). A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch Gen Psychiatry, 54*(9), 877-885.

Brent, D. A., Kolko, D. J., Birmaher, B., Baugher, M., & Bridge, J. (1999). A clinical trial for adolescent depression: predictors of additional treatment in the acute and follow-up phases of the trial. *J Am Acad Child Adolesc Psychiatry, 38*(3), 263-270; discussion 270-261.

Brent, D. A., Oquendo, M., Birmaher, B., Greenhill, L., Kolko, D., Stanley, B., et al. (2002). Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. *Arch Gen Psychiatry, 59*(9), 801-807.

Brooks, R. (1996). EuroQol:the current state of play. *Health Policy, 37*, 53-72.

Byford, S., Barrett, B., Dubicka, B., Wilkinson, P., Kelvin, K., Roberts, C., et al. (2007). Cost-effectiveness of fluoxetine and cognitive-behaviour therapy versus fluoxetine alone in adolescents with major depression. *BMJ*.

Byford, S., Harrington, R., Torgerson, D., Kerfoot , M., Dyer, E., Harrington, V., et al. (1999). Cost-effectiveness analysis of a home-based social work intervention for children and adolescents who have deliberately poisoned themselves: results of a randomised controlled trial. *British Journal Psychiatry, 174*, 56-62.

Clarke, G., Debar, L., Lynch, F., Powell, J., Gale, J., O'Connor, E., et al. (2005). A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry, 44*(9), 888-898.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioural Sciences.* Hillsdale, New Jersey.: Lawrence Erlbaum Associates, Inc.,.

Curtis, L., & Netten , A. (2004). *Unit costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit.

Daley, S. E., Rizzo, C. J., & Gunderson, B. H. (2006). The longitudinal relation between personality disorder symptoms and depression in adolescence: the mediating role of interpersonal stress. *J Personal Disord, 20*(4), 352-368.

DAMOCLES, S. G. (2005). A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*, 711-722.

Daviss, W. B., Birmaher, B., Melhem, N. A., Axelson, D. A., Michaels, S. M., & Brent, D. A. (2006). Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. *J Child Psychol Psychiatry, 47*(9), 927-934.

Drummond, M. F., O'Brien, B., & Stoddart , G. L. (2005). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford:: Oxford University Press.

Dunn, V., & Goodyer, I. M. (2006). Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. *Br J Psychiatry, 188*, 216-222.

Efron, B., & Tibshirani, R. J. (1993). *An introduction to the bootstrap*. New York: Chapman & Hall.

Eisenberg, J. M. (1989). Clinical economics: a guide to the economic analysis of clinical practices. *JAMA, 262:*, 2879-2886.

Fava, G. A., Ruini, C., Rafanelli, C., Finos, L., Conti, S., & Grandi, S. (2004). Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *Am J Psychiatry, 161*(10), 1872-1876.

Fenwick , E., Claxton, K., & Sculpher, M. (2001). Representing uncertainty: the role of cost-effectiveness SCCeptability curves. *Health Economics, 10*, 779-787.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *Structured clinical interview for DSM-IV Personality Disorders, SCID II.* Washington D. C.: American Psychiatric Press.

Fombonne, E., Wostear, G., Cooper, V., Harrington, R., & Rutter, M. (2001). The Maudsley long-term follow-up of child and adolescent depression. 2. Suicidality, criminality and social dysfunction in adulthood. *British Journal of Psychiatry, 179*, 218-223.

Fonagy, P., Gergely, G., Jurist, E., & Target, M. (2002). *Affect Regulation, Mentalization and the Development of the Self.* New York: Other Press.

Fonagy, P., Miller, J. M., Edgcumbe, R., Target, M., & Kennedy, H. (1993). *The Hampstead Manual of Psychodynamic Developmental Therapy for Children*.Unpublished manuscript, London.

Fonagy, P., & Target, M. (1994). The efficacy of psychoanalysis for children with disruptive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 33*, 45-55.

Fonagy, P., & Target, M. (1996a). Predictors of outcome in child psychoanalysis: a retrospective study of 763 cases at the Anna Freud Centre. *J Am Psychoanal Assoc, 44*(1), 27-77.

Fonagy, P., & Target, M. (1996b). Predictors of outcome in child psychoanalysis: A retrospective study of 763 cases at the Anna Freud Centre. *Journal of the American Psychoanalytic Association, 44*, 27-77.

Goodyer, I. M., Dubicka, B., Wilkinson, P., Kelvin, K., Roberts, C., Byford, S., et al. (2007). ADAPT: A Randomised Controlled Trial of SSRIs with and without cognitive behaviour therapy in adolescents with major depression. *British Medical Journal*.

Goodyer, I. M., Herbert, J., & Tamplin, A. (2003). Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. *Psychol Med, 33*(4), 601-610.

Gowers, S., Levine, W., Bailey-Rogers, S., Shore, A., & Burhouse, E. (2002). Use of a routine, self-report outcome measure (HoNOSCA-SR) in two adolescent mental health services. Health of the Nation Outcome Scale for Children and Adolescents. *Br J Psychiatry, 180*, 266-269.

Harrington, R., Kerfoot, M., Dyer, E., McNiven, F., Gill, J., Harrington, V., et al. (1998). Randomized trial of a home-based family intervention for children who have deliberately poisoned themselves. *J Am Acad Child Adolesc Psychiatry, 37*(5), 512-518.

Harrington, R., Peters, S., Green, J., Byford , S., Woods, J., & McGowan, R. (2000). Randomised comparison of the effectiveness and costs of community and hospital based mental health services for children with behavioural disorders. *British Medical Journal, 321*, 1047-1050.

Harrington, R., Whittaker, J., Shoebridge, P., & Campbell, F. (1998). Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder. *Bmj, 316*(7144), 1559-1563.

Harrington, R. C., & Clark, A. (1998). Prevention and early intervention for depression in adolescence and early adult life. *Eur Arch Psychiatry Clin Neurosci, 248*, 32-45.

Harrington, R. C., & Dubicka, B. (2001). Natural history of mood disorders in children and adolescents. In I. Goodyer (Ed.), *The Depressed Child and Adolescent* (2 ed., pp. 311-343). Cambridge: Cambridge University Press.

Harrington, R. C., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1990). Adult Outcomes of Childhood and Adolescent Depression I. Psychiatric Status. *Archives of General Psychiatry, 47*(5), 465-473.

Heinicke, C. M., & Ramsey-Klee, D. M. (1986). Outcome of child psychotherapy as a function of frequency of sessions. *Journal of the American Academy of Child Psychiatry,, 25*, 247-253.

Herbert, J., Goodyer, I. M. et al. (2006). Do corticosteroids damage the brain? J Neuroendocrinol 18(6): 393-411.

Hill, C. E., O'Grady, K. E., & Elkin, I. (1992). Applying the collaborative study psychotherapy rating scale to rate therapist adherence in cognitive-behaviour therapy, interpersonal therapy, and clinical management. *J Consult Clin Psychol, 60*, 73-79.

Horvath, A. O., & Luborsky, L. (1993). The role of the therapeutic alliance in psychotherapy. *J Consult Clin Psychol, 61*(4), 561-573.

Johannesson, M. (1995). A note on the depreciation of the societal perspective in economic evaluation of health care. *Health Policy, 33*, 59-66.

Johnson, J. G., Cohen, P., Skodol, A. E., Oldham, J. M., Kasen, S., & Brook, J. S. (1999). Personality disorders in adolescence and risk of major mental disorders and suicidality during adulthood. *Arch Gen Psychiatry, 56*(9), 805-811.

Jones, E. E. (2000). *Therapeutic Action: A Guide to Psychoanalytic*
Therapy. Northvale, NJ: Jason Aronson.

Kaufman, J., Birmaher, B., Brent, D. A., Ryan, N. D., & Rao, U. (2000). The K-Sads-Present and LIfetime Version. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(10), 1208.

Kolvin, I., Garside, R. F., Nicol, A. R., MacMillan, A.,, Wolstenholme, F., & Leitch, I. M. (1981). *Help Starts Here: The Maladjusted Child in the Ordinary School.* London: Tavistock.

Kolvin, I., MacMillan, A., & Wrate, R. M. (1988). Psychotherapy is effective. *Journal of the Royal Society of Medicine, 81*, 261-266.

Koopmanschap, M., & Rutten, F. (1996). A practical guide for calculating indirect costs of disease. *Pharmacoeconomics, 10*, 460-466.

Kotte, A., McQuaid, J. R. et al. (2007). Psychotherapeutic mechanisms of change: the role of genes in depression treatment outcome. The American Society of Human Genetics 57th Annual Meeting, San Diego, CA.

Langbehn, D. R., Pfohl, B. M., Reynolds, S., Clark, L. A., Battaglia, M., Bellodi, L., et al. (1999). The Iowa Personality Disorder Screen: development and preliminary validation of a brief screening interview. *J Personal Disord, 13*(1), 75-89.

Layard, R. (2006). *Mental Health: Britains Biggest Social Problem*: Department of Health.

Lee, K. J., & Thompson, S. G. (2005). Clustering by health professional in individually randomised trials. *Bmj, 330*(7483), 142-144.

Lush, D., Boston, M., & Grainger, E. (1991). Evaluation of psychoanalytic psychotherapy with children: Therapists' assessments and predictions. *Psychoanalytic Psychotherapy, 5*, 191-234.

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., et al. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *Jama, 292*(7), 807-820.

McCullagh, P. (1980). Regression models for ordinal data. *J Roy Stat Soc, 43*, 109-142.

McMahon, F. J., S. Buervenich, et al. (2006). Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet 78(5): 804-14.

Miller, J. M. (1993). *The Manualization of Child Psychoanalysis.* Unpublished Ph.D., University of London.

Moran, G., Fonagy, P., Kurtz, A., Bolton, A., & Brook, C. (1991). A controlled study of the psychoanalytic treatment of brittle diabetes. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*, 926-935.

Mufson, L., Dorta, K. P., Wickramaratne, P., Nomura, Y., Olfson, M., & Weissman, M. M. (2004). A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry, 61*(6), 577-584.

Muratori, F., Picchi, L., Bruni, G., Patarnello, M., & Romagnoli, G. (2003). A two-year follow-up of psychodynamic psychotherapy for internalizing disorders in children. *J Am Acad Child Adolesc Psychiatry, 42*(3), 331-339.

Muratori, F., Picchi, L., Casella, C., Tancredi, R., Milone, A., & Patarnello, M. G. (2001). Efficacy of brief dynamic psychotherapy for children with emotional disorders. *Psychotherapy and Psychosomatics, 71*, 28-38.

Myers, K., McCauley, E., Calderon, R., & Treder, R. (1991). The 3-year longitudinal course of suicidality and predictive factors for subsequent suicidality in youths with major depressive disorder. *J Am Acad Child Adolesc Psychiatry, 30*(5), 804-810.

Newton-Howes, G., Tyrer, P., & Johnson, T. (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. *Br J Psychiatry, 188*, 13-20.

Nolen-Hoeksema, S. and Morrow, J. (1991). A Prospective Study of Depression and Posttraumatic Stress Symptoms After a Natural Disaster: The 1989 Loma Prieta Earthquake. Journal of Personality and Social Psychology 61(1): 115-121.

O'Hara, R., C. M. Schroder, et al. (2007). Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. Mol Psychiatry 12(6): 544-55.

Park, R. J., Goodyer, I. M., & Teasdale, J. D. (2005). Self-devaluative dysphoric experience and the prediction of persistent first-episode major depressive disorder in adolescents. *Psychol Med, 35*(4), 539-548.

Paykel, E. S. (2006). Cognitive therapy in relapse prevention in depression. *Int J Neuropsychopharmacol*, 1-6.

Paykel, E. S., Scott, J., Cornwall, P. L., Abbott, R., Crane, C., Pope, M., et al. (2005). Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. *Psychol Med, 35*(1), 59-68.

Petri, H., & Thieme, E. (1978). Katamnese zur analytischen psychotherapie im kindes und jugendalter. *Psyche, 1*, 21-54.

Poznanski, E. O., Freman, L. N., & Mokros, H. B. (1985). Children's depression rating scale-revised. *Psychopharmacol Bull, 21*, 979-989.

Puig-Antich, J., Kauffman, J., & Ryan, N. (1993). The psychosocial functioning and family environment of depressed children. *Journal of the American Academy of Child and ASdolescent Psychiatry, 32*, 244-254.

Rance, S. (2003). Report on the Survey of ACP Members about the

Outcome Study. Part II: Summary of Therapist Activity and Child Data. *Bulletin of the Association of Child Psychotherapists, 133*, 25-32.

Rao, U., Weissman, M. M., Martin, J. A., & ., e. a. (1993). Childhood depression and risk of suicide: preliminary report of a longitudinal study. *J Am Acad Child Adolesc Psychiatry, 32*, 21-27.

Reid, S., Alvarez, A., & Lee, A. (2001). The Tavistock Autism Workshop Approach. In J. Richer & S. Coates (Eds.), *Autism-The Search for Coherence* (pp. 182-192). London: Jessica.

Roberts, C. (1999). The implications of variation in outcome between health professionals for the design and analysis of randomized controlled trials. *Statistics in Medicine, 18:*, 2605-2615.

Roberts, C., & Roberts, S. A. (2005). Design and analysis of clinical trials with clustering effects due to treatment. *Clinical Trials, 2*, 152-162.

Robin, A. L., Siegel, P. T., Moye, A. W., Gilroy, M., Dennis, A. B., & Sikand, A. (1999). A controlled comparison of family versus individual therapy for adolescents with anorexia nervosa. *J Am Acad Child Adolesc Psychiatry, 38*(12), 1482-1489.

Romeo, R., Byford, S., & Knapp, M. (2005). Annotation: Economic evaluations of child and adolescent mental health interventions: a systematic review. *J Child Psychol Psychiatry, 46*(9), 919-930.

Roth, A., & Fonagy, P. (2004). *What works for whom? A critical review of psychotherapy research.*

Sandler, J., Kennedy, H., & Tyson, R. (1980). *The Technique of Child Analysis: Discussions with Anna Freud*. London: Hogarth Press.

Scott, J., Palmer, S., Paykel, E., Teasdale, J., & Hayhurst, H. (2003). Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. *Br J Psychiatry, 182*, 221-227.

Scott, J., Teasdale, J. D., Paykel, E. S., Johnson, A. L., Abbott, R., Hayhurst, H., et al. (2000). Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. *Br J Psychiatry, 177*, 440-446.

Shaffer, D., Gould, M. S., Brasic, J., & al., e. (1983). A children's Global Assessment Scale (C-GAS). *Arch Gen Psychiatry, 40*, 1228-1231.

Sherwin-White, S., Shuttleworth, A., Tydeman, B., & Urwin, C. (2003). *The Work of Child Psychotherapists in the NHS: Generic and Specialist Contributions to the Multi-Disciplinary Teams.* London:: Association of Child Psychotherapists.

Shirk, S. R., & Karver, M. (2003). Prediction of treatment outcome from relationship variables in child and adolescent therapy: a meta-analytic review. *J Consult Clin Psychol, 71*(3), 452-464.

Sinha, U. K., & Kapur, M. (1999). Psychotherapy with emotionally disturbed adolescent boys: Outcome and process study. *NIMHANS Journal,, 17*, 113-130.

Smits, K. M., Smits, L. J. et al. (2004). Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review. Mol Psychiatry 9(5): 433-41.

Smyrnios, K. X., & Kirkby, R. J. (1993). Long-term comparison of brief versus unlimited psychodynamic treatments with children and their parents. *J Consult Clin Psychol, 61*(6), 1020-1027.

Target, M., & Fonagy, P. (1994a). Efficacy of psychoanalysis for children with emotional disorders. *J Am Acad Child Adolesc Psychiatry, 33*(3), 361-371.

Target, M., & Fonagy, P. (1994b). The efficacy of psychoanalysis for children: Developmental considerations. *Journal of the American Academy of Child and Adolescent Psychiatry, 33*, 1134-1144.

Target, M., & Fonagy, P. (2002). The long-term follow-up of child analytic treatments (AFC3). In P. Fonagy (Ed.), *An open door review of outcome studies in psychoanalysis.* (2 ed., pp. 141-146). London: International Psychoanalytic Association.

Teasdale J.D., Cox S.G. (2001). Dysphoria: self-devaluative and affective components in recovered depressed patients and never depressed controls. *Psychol Med,* 31,1311-6.

Trowell, J., Joffe, I., Campbell, J., Clemente, C., Almqvist, F., Soininen, M., et al. (2007). Childhood depression: a place for psychotherapy: an outcome study comparing Individual Psychodynamic Psychotherapy and Family Therapy. *Eur Child Adolesc Psychiatry*.

Trowell, J., Kolvin, I., Weeramanthri, T., Sadowski, H., Berelowitz, M., Glaser, D., et al. (2002). Psychotherapy for sexually abused girls: psychopathological outcome findings and patterns of change. *Br J Psychiatry, 180,* 234-247.

Van Hout, B. A., Al, M. J., G.S., G., & Rutten, F. F. H. (1994). Costs, effects and c/e-ratios alongside a clinical trial. *Health Economics, 3*, 309-319.

Vilsvik, S. O., & Vaglum, P. (1990). Teenage Anorexia Nervosa: A 1 to 9 year follow up after psychodynamic treatment. *Nord Psykiatr Tidsskr, 44*, 249-255.

Weersing, V. R., Iyengar, S., Kolko, D. J., Birmaher, B., & Brent, D. A. (2006). Effectiveness of cognitive-behavioral therapy for adolescent depression: a benchmarking investigation. *Behav Ther, 37*(1), 36-48.

Weiss, B., Catron, T., & Harris, V. (2000). A 2-year follow-up of the effectiveness of traditional child psychotherapy. *J Consult Clin Psychol, 68*(6), 1094-1101.

Weisz, J. R. (2004). *Psychotherapy for Children and Adolescents:*
Evidence-Based Treatments and Case Examples. Cambridge: Cambridge University Press.

Wilkinson, P. O., & Goodyer, I. M. (2006). Attention difficulties and mood-related ruminative response style in adolescents with unipolar depression. *J Child Psychol Psychiatry, 47*(12), 1284-1291.

Wilkinson, P. (2007). Attention and Thinking Styles in Depressed Adolescents. MD Thesis, University of Cambridge.

Wilkinson, P. and I. Goodyer, I. M. (2008). The Effects of Cognitive-Behavioural Therapy on Mood-Related Ruminative Response Style in Depressed Adolescents. Child and Adolescent Psychiatry and Mental Health, 2, 3.

Winkelmann, K., Hartmann, M., Neumann, K., Hennch, C., Reck, C., Victor, D., et al. (2000). Stability of therapeutic outcome after child and adolescent psychoanalytical therapy. *Praxis Kinderpsychol Kinderpsychiatr, 49*, 315-328.

Wood, A. J., Harrington, R. C., & Moore, A. (1996). Controlled trial of brief cognitive-behavioural intervention in adolescent patients with depressive disorders. *Journal of Child Psychology and Psychiatry, 37,* 737-746.

Young, J. F., Mufson, L., & Davies, M. (2006). Efficacy of Interpersonal Psychotherapy-Adolescent Skills Training: an indicated preventive intervention for depression. *J Child Psychol Psychiatry, 47*(12), 1254-1262.

Flow Chart for the Study