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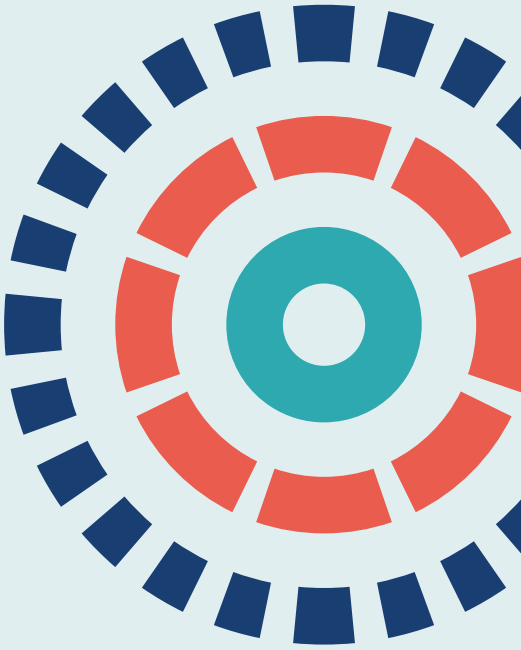

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Abstract

Social recovery therapy for young people with emerging severe mental illness: the Prodigy RCT

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Background: Young people with social disability and non-psychotic severe and complex mental health problems are an important group. Without intervention, their social problems can persist and have large economic and personal costs. Thus, more effective evidence-based interventions are needed. Social recovery therapy is an individual therapy incorporating cognitive–behavioural techniques to increase structured activity as guided by the participant's goals.

Objective: This trial aimed to test whether or not social recovery therapy provided as an adjunct to enhanced standard care over 9 months is superior to enhanced standard care alone. Enhanced standard care aimed to provide an optimal combination of existing evidence-based interventions.

Design: A pragmatic, single-blind, superiority randomised controlled trial was conducted in three UK centres: Sussex, Manchester and East Anglia. Participants were aged 16–25 years with persistent social disability, defined as < 30 hours per week of structured activity with social impairment for at least 6 months. Additionally, participants had severe and complex mental health problems, defined as at-risk mental states for psychosis or non-psychotic severe and complex mental health problems indicated by a Global Assessment of Functioning score ≤ 50 persisting for ≥ 6 months. Two hundred and seventy participants were randomised 1 : 1 to either enhanced standard care plus social recovery therapy or enhanced standard care alone. The primary outcome was weekly hours spent in structured activity at 15 months post randomisation. Secondary outcomes included subthreshold psychotic, negative and mood symptoms. Outcomes were collected at 9 and 15 months post randomisation, with maintenance assessed at 24 months.

Results: The addition of social recovery therapy did not significantly increase weekly hours in structured activity at 15 months (primary outcome treatment effect −4.44, 95% confidence interval −10.19 to 1.31). We found no evidence of significant differences between conditions in secondary

outcomes at 15 months: Social Anxiety Interaction Scale treatment effect −0.45, 95% confidence interval −4.84 to 3.95; Beck Depression Inventory-II treatment effect −0.32, 95% confidence interval −4.06 to 3.42; Comprehensive Assessment of At-Risk Mental States symptom severity 0.29, 95% confidence interval −4.35 to 4.94; or distress treatment effect 4.09, 95% confidence interval −3.52 to 11.70. Greater Comprehensive Assessment of At-Risk Mental States for psychosis scores reflect greater symptom severity. We found no evidence of significant differences at 9 or 24 months. Social recovery therapy was not estimated to be cost-effective. The key limitation was that missingness of data was consistently greater in the enhanced standard care-alone arm (9% primary outcome and 15% secondary outcome missingness of data) than in the social recovery therapy plus enhanced standard care arm (4% primary outcome and 9% secondary outcome missingness of data) at 15 months.

Conclusions: We found no evidence for the clinical superiority or cost-effectiveness of social recovery therapy as an adjunct to enhanced standard care. Both arms made large improvements in primary and secondary outcomes. Enhanced standard care included a comprehensive combination of evidence-based pharmacological, psychotherapeutic and psychosocial interventions. Some results favoured enhanced standard care but the majority were not statistically significant. Future work should identify factors associated with the optimal delivery of the combinations of interventions that underpin better outcomes in this often-neglected clinical group.

Trial registration: Current Controlled Trials ISRCTN47998710.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta25700).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

Glossary

Acceptance and Avoidance Questionnaire II A brief self-report measure of the presence or absence of experiential avoidance/psychological inflexibility (unwillingness to experience one's own negative thoughts or emotions).

Alcohol Use Disorders Identification Test A brief self-report measure capturing the presence or absence of levels of harmful alcohol use.

Assertive outreach A model of care for people with complex needs that emphasises flexible engagement and visiting people in community settings.

At-risk mental states A state or phase in which a person is considered to have an elevated risk of developing psychosis. At-risk mental states include attenuated symptoms of psychosis and may include changes in mood, cognition, thought content and behaviours.

Attenuated symptoms of psychosis Experiences such as mild confusion in thinking, suspiciousness, odd beliefs and perceptual distortions that are not quite of psychotic intensity or frequency.

Beck Depression Inventory-II A brief self-report measure capturing the presence or absence of symptoms associated with depression.

Beck Hopelessness Scale A brief self-report measure capturing the presence or absence of hopelessness.

Brief Core Schema Scale A brief self-report measure capturing the presence or absence of positive and negative evaluations of oneself and other people.

Child and Adolescent Mental Health Services/Children and Young People's Services NHS mental health services for children and young people, generally provided until the age at which compulsory education would cease.

Cognitive Therapy Rating Scale Revised A brief measure focusing on competent use of cognitive–behavioural therapy.

Comprehensive Assessment of At-Risk Mental States A structured mental state interview conducted by a trained assessor that is used to assess attenuated psychotic symptoms and associated psychopathology, drug use, and risk to self and others.

Constructive economic activity Scored from the Time Use Survey; a measure of hours spent in paid or voluntary work, education, child or other caring activities, and household chores.

Controlled Oral Word Association Test A brief neuropsychological assessment conducted by a trained assessor in which people verbally generate words beginning with a given letter in 60-second trials.

Drug Use Disorders Identification Test A brief self-report measure capturing the presence or absence of levels of harmful drug use.

Early Intervention in Psychosis A model of care provision for young people (typically aged $\geq$ 14 years, although this is variable nationally) during and for 2–4 years after the first episode of psychosis. The model of care involves care co-ordination and medical, psychological and psychosocial intervention.

EuroQol-5 Dimensions A brief generic self-report measure of quality of life.

Global Assessment of Functioning A 0–100 scale rated by a trained assessor that captures the presence or absence of severe symptoms of at least two out of depression, anxiety, substance misuse, behavioural or thinking problems, or subthreshold psychosis to the degree that they impair function.

Health Service Resource Use Questionnaire A brief self-report measure capturing use of physical health and mental health support services modified from the Client Service Receipt Inventory.

Logical Memory I A brief neuropsychological assessment conducted by a trained assessor in which people verbally recall a short story immediately after its auditory presentation by the assessor.

Meaning in Life Questionnaire Brief self-report measure assessing the perception of searching for and of experiencing meaning and purpose within one's life.

Multisystemic A model of care that focuses on working with the systems around a young person, including family, peers, school and community.

National Pupil Database Contains detailed information about pupils in schools and colleges in England.

Scale for Assessment of Negative Symptoms A scale scored by a trained assessor evaluating the presence or absence of symptom domains including affective blunting, apathy, impoverished thinking, asociality and disturbance of attention.

Schizotypal Symptoms Inventory A brief self-report measure capturing the presence or absence of unusual and anomalous experiences, including paranoia.

Social Interaction Anxiety Scale A brief self-report measure capturing the presence or absence of social anxiety.

Structured Activity Scored from the Time Use Survey; a measure of hours spent in constructive economic activity plus structured leisure and sports activities.

Structured Clinical Interview A structured clinical interview conducted by a trained assessor designed to categorise symptoms and experiences according to the major diagnoses from the *Diagnostic and Statistical Manual of Mental Disorders*.

Time Use Survey Derived from the Office for National Statistics' Time Use Survey, this is an established measure with good psychometric properties that assesses hours per week engaged in constructive economic and structured activity. Data are captured within a semistructured interview conducted by a trained assessor and scored in the metric of hours of activity.

Trait Hope Scale A brief self-report measure capturing the presence or absence of the general trait hopefulness. This measure is presented as 'The Future Scale' to participants.

List of abbreviations

AE	adverse event
APS	attenuated psychotic symptoms
ARMS	at-risk mental states for psychosis
AUDIT	Alcohol Use Disorders Identification Test
BHS	Beck Hopelessness Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States for psychosis
CAMHS	Child and Adolescent Mental Health Services
CBT	cognitive–behavioural therapy
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COWAT	Controlled Oral Word Association Test
CSRI	Client Services Receipt Inventory
CTRS-R	Cognitive Therapy Rating Scale Revised
DMEC	Data Monitoring and Ethics Committee
DUDIT	Drug Use Disorders Identification Test
EDIE-2	Early Detection and Intervention Evaluation for people at high-risk of psychosis 2 trial
EIP	Early Intervention in Psychosis
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
ESC	enhanced standard care
FEP	first-episode psychosis
FIML	full information maximum likelihood
GAF	Global Assessment of Functioning
GAS	Global Assessment of Symptoms
GP	general practitioner
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
MI	multiple imputation
NCTU	Norwich Clinical Trials Unit
NEET	not in education, employment or training
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAT	PRODIGY Advisory Team
PIS	participant information sheet
PP	per protocol
PPI	patient and public involvement
PSS	Personal Social Services
QALY	quality-adjusted life-year
RA	research assistant
REC	Research Ethics Committee
SA1	sensitivity analysis 1
SA2	sensitivity analysis 2
SAE	serious adverse event
SANS	Scale for the Assessment of Negative Symptoms
SD	standard deviation
SIAS	Social Interaction Anxiety Scale
SOFAS	Social and Occupational Functioning Assessment Scale
SRT	social recovery therapy
SSI	Schizotypal Symptoms Inventory
TDMS	trial data management system
TSC	Trial Steering Committee
TUS	Time Use Survey
UHR	ultra-high risk

Plain English summary

Young people with social disability and non-psychotic severe and complex mental health problems are an important group. Their problems are often long-standing and they often have difficulty doing 'structured activity', such as work, sports and leisure activities (e.g. going shopping or to the cinema). They often avoid such activities because of anxiety or low mood. Other barriers may include financial and practical issues, and stigma from activity providers. Non-participation in structured activity increases the risk that mental health problems will continue and prevent these young people from reaching meaningful goals.

We tested whether or not social recovery therapy might help. This is a talking and activity therapy, in which young people (participants) work individually with a social recovery therapy therapist. Social recovery therapy aims to help participants identify what activities they would like to do, practise spending more time doing them, and work through barriers to maintaining increased activity. By improving structured activity, young people feel more hopeful and better able to manage their symptoms. However, social recovery therapy has never been evaluated properly using the best research methods. The best way to evaluate treatments like this is a randomised controlled trial in which participants are allocated by chance, like tossing a coin, to have the new therapy or not to have the therapy. Both groups are followed up for a period to see if the new therapy works. We tested social recovery therapy in this way. We also tested whether or not it was cost-effective.

We recruited 270 16- to 25-year-old participants in Sussex, East Anglia and Manchester. Participants had non-psychotic severe and complex mental health problems (not psychosis) and were doing < 30 hours of structured activity per week at the start of the study. All participants had enhanced standard care. This involved standard NHS treatment plus a full assessment and feedback from the study team, and a best practice guide to local support services that encouraged the best provision of standard evidence-based interventions. Half of the participants were randomly allocated to have social recovery therapy in addition to enhanced standard care over 9 months. All participants were invited to assessments 9, 15 and 24 months later. Therapists recorded the tasks and activities undertaken with participants. We asked both participants and therapists what they thought of the trial and the social recovery therapy.

We found no evidence that adding social recovery therapy improved outcomes. Participants in both arms made large and clinically worthwhile improvements in structured activity and mental health outcomes. If anything, there was some evidence that people allocated to enhanced standard care improved more than those allocated to social recovery therapy plus enhanced standard care. The differences were small, however, and could have occurred by chance.

Scientific summary

Text in this section reproduces material in the published trial protocol. [Reproduced with permission from Fowler D, French P, Banerjee R, Barton G, Berry C, Byrne R, *et al.* Prevention and treatment of long-term social disability amongst young people with emerging severe mental illness with social recovery therapy (The PRODIGY Trial): study protocol for a randomised controlled trial. *Trials* 2017;**18**:315. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated. The text below includes minor additions and formatting changes to the original text.]

Background

Young people who have social disability associated with non-psychotic severe and complex mental health problems are an important group in need of early intervention. Their problems are often long-standing and evident from an early age. They have a high risk of long-term and serious mental health problems and social disability. Without intervention, the long-term prognosis is poor and the economic costs are large. There is a gap in the provision of evidence-based interventions for this group, and new approaches are needed. We aimed to evaluate a new approach to early intervention with young people with social disability and non-psychotic severe and complex mental health problems using social recovery therapy over a period of 9 months to improve mental health and social recovery outcomes, and to compare it with enhanced standard care.

Objectives

To undertake a definitive randomised trial to determine the clinical effectiveness and cost-effectiveness of social recovery therapy compared with enhanced standard care in young people who present with social withdrawal and non-psychotic severe and complex mental health problems, and who are at risk of long-term social disability and mental illness.

The primary hypothesis was that, for young people who are socially disabled and have non-psychotic severe and complex mental health problems, social recovery therapy plus enhanced standard care would be superior to enhanced standard care alone in improving social recovery (as measured by hours in structured activity assessed on the Time Use Survey) over a 15-month follow-up period. Secondary hypotheses were, first, that social recovery therapy plus enhanced standard care would be superior to enhanced standard care alone in terms of cost-effectiveness and, second, that social recovery therapy plus enhanced standard care would be superior to enhanced standard care alone in effects on mental health symptoms (attenuated psychotic symptoms and emotional disturbance).

Methods

This was a pragmatic, multicentre, single-blind, superiority randomised controlled trial. It was conducted in three sites in the UK: Sussex, Manchester and East Anglia. Participants were recruited between 2012 and 2017. Inclusion criteria were that participants (1) were aged 16–25 years; (2) had persistent social

disability operationalised as structured and constructive economic activity of < 30 hours per week and a history of social impairment problems lasting for at least 6 months; and (3) had severe and complex mental health problems operationalised as (a) meeting at-risk mental states for psychosis criteria, or (b) non-psychotic mental health problems scoring ≤ 50 on the Global Assessment of Functioning scale (indicating the presence of severe symptoms of at least two out of depression, anxiety, substance misuse, thinking or behavioural problems) with at least moderate symptoms (operationalised as a Global Assessment of Functioning score < 60) persisting for a period of at least 6 months. Exclusion criteria were current or historical psychosis, severe learning disability, presence of disease, physical problems, or non-English speaking to a degree that interferes with the capacity to consent to and participate in the research.

The sample size was 270 participants, providing 135 participants per trial arm. An effect size of 0.4 standard deviations was considered a minimum clinically significant benefit, with 270 participants providing > 90% power to detect this effect with a two-sided 5% significance level. Participants were randomised 1 : 1 using a web-based randomisation system and allocated to either social recovery therapy plus optimised treatment as usual (enhanced standard care) or enhanced standard care alone. The primary outcome was time use, namely hours spent in structured activity per week at 15 months post randomisation. Secondary outcomes assessed typical mental health problems of the group, including subthreshold psychotic symptoms, negative symptoms, depression and anxiety. Time use, secondary outcomes and health economic measures were assessed at 9 and 15 months. Maintenance of outcome was assessed in a separate study at 24 months. The main trial results were tested using general linear models, with site as a random factor, and adjusting for stratification variables and neurocognitive performance. Maintenance of gains was tested using available data at 24 months.

Three qualitative process evaluation substudies were conducted. The first captured participants' perspectives on their experiences of the research processes, including assessment involvement and contact with the research team. The second captured patient perspectives, but focused primarily on experiences of allocation, provision and involvement in social recovery therapy and enhanced standard care intervention. Both patient process evaluation substudies were interview-based, using thematic analytic methods, and were conducted by a sub-research team co-led by an independent qualitative researcher, user researcher and members of the trial team. The final process evaluation focused on social recovery therapy therapist experience of working with complex clients. This was an interview study using an Interpretative Phenomenological Analysis methodology and was led by trial team members who were not involved in the original inception of social recovery therapy or the present study.

Results

In total, 942 young people were referred. From this group, 298 young people were not appropriate referrals, 194 young people were not interested in becoming involved in the research and six young people declined to consent. Therefore, 444 young people were assessed for eligibility, 174 of whom were not eligible, including 27 who did not complete the assessment process. Of the 270 randomised participants, there were 241 participants retained at 9 months, 235 participants at 15 months and 206 participants at 24 months.

We found no evidence that social recovery therapy was superior to enhanced standard care on the primary outcome of weekly hours spent in structured activity at 15 months (Time Use Survey) (treatment effect −4.44, 95% confidence interval −10.19 to 1.31). We found no evidence of significant differences between trial arms in secondary outcomes at the primary end point of 15 months: Social Anxiety Interaction Scale treatment effect −0.45, 95% confidence interval −4.84 to 3.95; Beck Depression Inventory-II treatment effect −0.32, 95% confidence interval −4.06 to 3.42; Comprehensive Assessment of At-Risk Mental States symptom severity treatment effect 0.29, 95% confidence interval −4.35 to 4.94;

or distress treatment effect 4.09, 95% confidence interval −3.52 to 11.70. Greater Comprehensive Assessment of At-Risk Mental States for psychosis scores reflect greater symptom severity. We found no evidence of significant differences at 9 or 24 months. Social recovery therapy was not estimated to be cost-effective.

On some dimensions there appeared to be mean differences favouring enhanced standard care over social recovery therapy plus enhanced standard care. However, the differences on the primary outcome and the majority of secondary outcomes did not meet the level for conventional significance, apart from social phobia and some subscales of negative symptoms at 15 months. At 24 months, mean differences on structured activity favoured enhanced standard care over social recovery therapy and enhanced standard care. Missingness of data was consistently higher in the enhanced standard care group than in social recovery therapy plus enhanced standard care group, and the bias and total amount of missingness of data increased over time. Although there were few data missing at 9 months (< 10%), at 15 months 20% of data on the primary outcome were missing and with a clear bias to greater missingness of data in the enhanced standard care group. At 24 months, > 30% data were missing and the amount of missingness of data in the enhanced standard care group was twice that in the social recovery therapy plus enhanced standard care group. It is plausible that differential missingness of data could bias results in favour of enhanced standard care, particularly at the later assessment stages. Although it is clear that there is no superiority for social recovery therapy, we are more cautious in concluding firmly that enhanced standard care alone was superior, even though there are trends in that direction.

There was a general pattern of large and clinically significant improvements over time in both the social recovery therapy plus enhanced standard care arm and the enhanced standard care-alone arm. There were large effect size gains in structured and constructive economic activity of > 10 hours per week in both arms. This is more than double the 4 hours constituting a clinically meaningful difference. There was a > 50% improvement in the rate of participants meeting diagnostic criteria for depression, panic, agoraphobia and social phobia in both groups and there were large effect gains in self-reported assessments of depression, social anxiety, hopelessness and schizotypal symptoms of paranoia and anomalous experiences, and negative symptoms. There were marked reductions in alcohol and drug use disorders.

The process evaluation suggested that participants valued both the research assessment process and social recovery therapy. Participants emphasised that social recovery therapy could be challenging to engage in and that the development of a positive therapeutic relationship with a social recovery therapy therapist was an essential aspect of the intervention. Participants emphasised, both in the research assessments and in social recovery therapy, the importance of discussing their experiences with another person. The process evaluation substudy with social recovery therapy therapists suggested that therapists could struggle with feelings of hopelessness in the context of therapy delivery with a group of young people characterised by ambivalence, a sense of being stuck and hopelessness. Nevertheless, adherence and competence data suggested that therapists delivered competent social recovery therapy, which was fully adherent to the therapy model in > 80% of cases.

Conclusions

The key conclusion of this study is that there was no evidence for the clinical superiority of social recovery therapy over enhanced standard care for any outcome, nor was there evidence of the cost-effectiveness of social recovery therapy. Both intervention groups made large and clinically significant gains in time use and across the spectra of social and mental health problem outcomes. Available data suggested that these gains were maintained in both groups of participants. There was an evident effect of the social recovery therapy intervention on participant engagement.

It was very notable that participants in the enhanced standard care-alone arm typically reported combinations of case management, psychological therapy, employment support, social care and youth support. In addition, the majority of participants reported taking psychiatric medication; therefore, enhanced standard care did not reflect the absence of intervention. The key clinical implication of this trial is, therefore, that if young people with non-psychotic severe and complex mental health problems and social disability are offered systematic intervention, then large and important gains in social and mental health outcomes are likely to occur. These services must be equipped to be able to manage the severity and complexity evident in this group of young people.

Recommendations for research include:

- The capture of engagement as an outcome of intervention – social recovery therapy had a clear effect on engagement and engagement itself is an important predictor of outcome and target for intervention. Future research could explore putative mechanisms of increased engagement and endeavour to isolate the key components of social recovery therapy (or other interventions) that have an impact on this.
- The capture of outcomes in absentia – the identification and operationalisation of meaningful outcomes that can be measured in the absence of face-to-face assessment is an important development to facilitate evaluating beneficial interventions for young people who struggle to engage with in-person research and clinical interactions.
- Investigation of person-centred treatment for young people with emerging non-psychotic severe and complex mental health problems – the current study reports no differences in group-level average effects of enhanced standard care versus enhanced standard care plus social recovery therapy. Future research should investigate what works for whom: the necessary and sufficient components of treatment for young people with emerging non-psychotic severe and complex mental health problems and social disability. The identification of subgroups of young people with emerging non-psychotic severe and complex mental health problems and social disability who respond differently to treatment as usual, for example subgroups that may be 'treatment resistant' and thus in need of more specialised interventions, are important for further research.

Trial registration

This trial is registered as ISRCTN47998710.

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Chapter 1 Introduction

Scientific background

It is now widely recognised that most socially disabling chronic and non-psychotic severe and complex mental health problems begin in adolescence, with 75% of all severe and chronic mental illnesses emerging between the ages of 15 and 25 years.[2,3] A series of retrospective studies have consistently shown that severe mental illness is often preceded by social decline, that this often becomes stable, and that such premorbid social disability is predictive of the long-term course of the disorder.[4] Between 3% and 5% of adolescents present with non-psychotic severe and complex mental health problems associated with social disability.[2] The young people at highest risk of long-term social disability present with emerging signs of social decline, in association with low-level psychotic symptoms and emotional and behavioural disorder often accompanied by substance misuse problems, and risk to self and others.[2,3]

Despite poor outcomes and the cost of disorders leading to social decline, young people with complex needs frequently do not access treatment, and less than 25% of young people and their families who have such needs access to specialist mental health services.[5–8] More complex cases are found in areas of social disadvantage and among those who are not in employment or education.[1] The economic costs of not addressing this disability are very high.[9] Persistent mental health problems associated with social disability in young people do not resolve naturally and may persist across the life course, resulting in severe distress and social disability, and high costs to health and a range of social and other services.[2,3] Health economic modelling of lifelong costs in this area is emerging. A recent estimate suggests that mental health problems in childhood and adolescence can result in problems across marital satisfaction, self-esteem and quality of life, and can lead to a 28% reduction in economic activity at age 50 years or a £388,000 lifetime loss per person.[10] Young people who have a combination of severe and persistent mental health needs and who are socially disabled present with problems that have the highest lifelong burden.

Several recent reports have highlighted that there is a major gap in identifying and managing the mental health problems of young people with non-psychotic severe and complex mental health problems, particularly those at risk of social disability.[5,7,8,11–13] New approaches to detection and intervention are required to meet the needs of these young people.[1] There is a gap in the evidence base for these young people.[1] Several National Institute for Health and Care Excellence (NICE) guidelines have highlighted this issue, including those for social anxiety,[14] depression,[15] and detection of people at risk of psychosis, and the research recommendation deriving from the NICE guideline on psychosis and schizophrenia in children and young people.[13]

Young people who have non-psychotic severe and complex mental health problems and who are socially disabled are complex. Thus, they tend not to be suitable for or respond to short-term evidence-based therapies for more discrete mental health problems, such as cognitive–behavioural therapy (CBT) for anxiety, depression and conduct disorder, which are available via the Improving Access to Psychological Therapies initiative. Moreover, although this group show clear evidence of social disability, they do not

meet the criteria for first-episode psychosis (FEP) and so they are not suitable for Early Intervention in Psychosis (EIP) services, for which there is now considerable evidence of benefits on social functioning.[4,16,17]

Our aim in the present project is to identify and target the group of young people who are socially disabled and have non-psychotic severe and complex mental health problems and are at risk of long-term severe mental illness to offer them a new psychological intervention specifically tailored to their needs.

The most systematic service provision is often outside mental health services in statutory and voluntary sector provision for young people who are not in education, employment or training (NEET). In these services, the focus is primarily on obtaining employment and, thus, the mental health problems that present barriers to activity, work, education and training may not be recognised.[18] However, the degree to which NEET status is associated with mental health problems is increasingly recognised.[18–24] Detection of this population therefore must focus on the screening of the mental health problems of young people who have links with NEET services and who are under primary mental health care, alongside seeking referrals from those referred to Child and Adolescent Mental Health Services (CAMHS) and adult services. This group may be detected in services for those in the at-risk mental states for psychosis (ARMS), where these services are present.

Current evidence for effective interventions to address social disability among young people in the early course of severe mental illness is very limited.[4] A series of studies have been undertaken that aimed to identify people at ultra-high risk (UHR) of poor long-term outcomes associated with severe mental illness, focusing predominantly on risk of psychosis.[25–28] The success of the UHR studies is that they have shown that it is possible to set up services to identify and treat cohorts of young people who can be identified as having ARMS using defined operational criteria and structured assessment tools.[29] Furthermore, these studies have consistently identified that those who are at the highest risk are young people who present with social decline as well as subthreshold psychotic symptoms.[30,31] However, the focus of these studies has been on prevention of episodes or symptoms of psychosis, not social disability.[1] Recent studies have shown that cohorts identified using these criteria may have more transient problems than previously thought and that only a subset go on to have long-term socially disabling mental health problems.[30,31] Several prominent UHR researchers are now highlighting an alternative strategy, which is to examine functional outcome in the UHR group. This study is consistent with this strategy.

Systematic reviews of CBT for psychosis, including NICE guidelines, have consistently shown a moderate effect size on improvements in social disability where this has been assessed as a secondary outcome.[32] This has been confirmed in the recent review of the NICE guidelines for schizophrenia.[33] However, these studies have predominantly been carried out among chronic participants, not young people.[1] The feasibility of using CBT with young people who are at UHR of long-term poor outcomes has been shown in the recently completed, multicentre Early Detection and Intervention Evaluation for people at high-risk of psychosis 2 (EDIE-2) trial,[34] which has shown reductions in the severity of psychotic symptoms. However, the focus of the therapy in EDIE-2[34] was symptom reduction,[28] and this approach neither targeted nor had a significant benefit on social disability. EDIE-2[34] clearly demonstrated the ability of collaborating sites to recruit young people at high risk and successfully retain them in research and therapy. However, as described above, the group recruited in EDIE-2[34] were heterogeneous in terms of social disability. The present trial builds on EDIE-2[34] by focusing on a group that has a more homogeneous set of social disability problems, defined by low-activity levels, and targeting this group with a multisystemic intervention that specifically aims to address social disability.

Better outcomes on social disability and hopelessness can be obtained from a more targeted intervention specifically focused on improving social disability among those who have low functioning. We have developed a multisystemic form of CBT that targets social disability.[35,36] A successful Medical Research Council trial[37] was carried out with a group of young people who had established chronic and severe social disability problems up to 8 years after a first episode of psychosis. This trial demonstrated gains

in structured activity and hope, as well as reductions in symptoms,[37] with evident long-term maintenance of gains in structured activity.[38] Clear indications of health economic benefits were demonstrated.[39] However, the trial was small and there was a high level of uncertainty associated with these estimates. A further, larger National Institute for Health Research (NIHR)-funded trial demonstrated gains in structured activity and reductions in symptoms for EIP service users who were experiencing their first episode of psychosis.[40]

The intervention used in this study has been refined from experience in previous studies to apply to socially withdrawn young people with non-psychotic severe and complex mental health problems.[35,36] The intervention is considered developmentally appropriate for young people owing to evident gains for young people accessing EIP services.[40] Moreover, social recovery therapy (SRT) is a collaborative approach, led by the young person's personally valued and meaningful goals.[36] This individualised goal focus means that SRT is in keeping with the adolescent and emerging adulthood stages of development, in which young people are beginning to individuate and separate from the family unit and to explore and develop their sense of self-identity.[41,42] Furthermore, SRT is in keeping with the youth perspective on social recovery, in which biographical disruption from mental health problems gives way to new meanings, identities and social connections.[43] To our knowledge, this trial was the first to specifically address both social disability and mental health problems among a high-risk population of young people presenting with social disability and non-psychotic severe and complex mental health problems.

Chapter 2 Methods

Aims and objective

We aimed to undertake a definitive randomised trial to determine the clinical effectiveness and cost-effectiveness of SRT plus enhanced standard care (ESC) compared with ESC alone in young people who present with social withdrawal and non-psychotic severe and complex mental health problems, and who are at risk of long-term social disability and mental illness.

The primary hypothesis was:

- In young people who are socially disabled and have non-psychotic severe and complex mental health problems, SRT plus ESC is superior to ESC alone in improving social recovery [as measured by hours in constructive economic activity assessed on the Time Use Survey (TUS)] over a 15-month follow-up period.

The secondary hypotheses were:

- SRT plus ESC is superior to ESC alone in terms of cost-effectiveness.
- SRT plus ESC is superior to ESC alone in terms of effects on mental health symptoms [attenuated psychotic symptoms (APS) and emotional disturbance].

Design

This was a pragmatic, multicentre, single-blind, superiority RCT with ascertainment of the clinical effectiveness and cost-effectiveness of SRT delivered over a 9-month period plus ESC compared with ESC alone in young people (aged 16–25 years) with non-psychotic severe and complex mental health problems and showing early signs of persistent social disability. Primary and secondary outcomes were evaluated at 15 months post randomisation (i.e. 6 months after the end of intervention or control) and limited assessment of longer-term outcomes was evaluated at 24 months post randomisation.

Procedure

Ethics approval was obtained from the former East of England Cambridgeshire and Hertfordshire National Research Ethics Service Committee for recruitment to an internal pilot (12/EE/0311) and the Preston Research Ethics Committee (REC) North West (15/NW/0590) for recruitment to the definitive trial. All participants provided written informed consent before undertaking any trial procedures.

Participants were recruited from child, adolescent and adult primary and secondary care mental health services (including youth mental health, early detection and early intervention services), and from youth, social, education and third-sector (i.e. voluntary, charitable and community) services. Potential participants were approached by their care provider and asked for agreement to be contacted by the study team.

Participants were provided with verbal and written information about the study using the participant information sheet (PIS) (see *Report Supplementary Material 1*). Interested participants were invited to provide written consent using an informed consent form (see *Report Supplementary Material 2*). Under supervision and review by the Trial Management Group, research assistants (RAs) administered eligibility screening assessments. Eligible participants completed the remaining baseline assessment measures, were randomised to the intervention or control arm of the trial, and were followed up over the following 24 months. All participants were offered a thorough assessment summary report for them and their usual care provider. For those participants randomly allocated to SRT in addition to ESC, a SRT therapist made contact within 1 week to inform participants of their allocation and to arrange the first therapy appointment. Participants' care providers (and referrers, if different) were informed of the allocation outcome.

Interventions

Social recovery therapy

The intervention was SRT plus ESC delivered by trial therapists who were clinical psychologists or qualified CBT therapists trained in the intervention. SRT is as described in a therapy manual.[36] SRT was delivered individually in face-to-face sessions, with interim telephone, text and e-mail contact. Sessions were delivered over 9 months. Sessions took place in participants' homes, NHS premises, community and public locations. All sessions, except where conducted in public locations, were audio-recorded with participant consent.

Social recovery therapy is based on a cognitive–behavioural model that suggests that social disability evolves as a result of lifestyle patterns of low activity, which are adopted as functional behavioural patterns of avoidance and are maintained by lack of hope, a reduced sense of agency and low motivation.[36] The intervention involves promoting a sense of hopefulness, self-agency and motivation, and encouraging activity, while managing any psychotic and non-psychotic symptoms and neurocognitive problems. The approach combines multisystemic working with the use of specific CBT techniques. Multisystemic working may involve working with participants' relatives and friends, and employment or education providers. Trial therapists adopt assertive outreach youth work principles and draw on successful social and vocational interventions, such as supported education and employment interventions.

Social recovery therapy involves three stages, which are flexibly tailored to each participant's goals and problems:

- Stage 1 involves assessment and developing a formulation of the person's difficulties and barriers to social recovery. This often involves validation of real barriers, threats and difficulties, while focusing on promoting hope for social recovery.
- Stage 2 involves identifying and working towards medium- to long-term goals guided by a multisystemic formulation of barriers to recovery. Identifying specific pathways to meaningful new activities and values is a central component of stage 2. This can include referral to appropriate vocational agencies and/or direct liaison with employers or education providers. Additional specific techniques used in stage 2 include cognitive work focused on promoting a sense of agency, consolidating a positive identity, and addressing feelings of stigma and negative beliefs about self and others.
- Stage 3 involves the active promotion of social, work, education and leisure activities linked to personally meaningful goals, while managing symptoms. This involves specific cognitive–behavioural techniques, including behavioural experiments.

Social recovery therapy adherence and competence

Therapist adherence and competence to the SRT intervention were recorded and reviewed. All SRT therapists completed the SRT adherence checklist[44] as soon as possible after each intervention session. The checklist involves indicating which components of the intervention were present during the session and briefly describing the delivery of this component to facilitate independent review.

This was in addition to all SRT therapists' recording their session notes, which further detailed the content of all SRT sessions and included additional records regarding all participant contacts beyond the sessions (including e-mail, telephone and text message contacts).

Social recovery therapy adherence was defined as follows:[44] (1) full dose equated to at least six sessions that included the presence of an assessment and a social recovery formulation, and that involved at least two pieces of behavioural work conducted in the community (i.e. not in the participant's home or a clinic room) with the therapist; (2) partial dose equated to at least six sessions, the presence of an assessment and formulation, and some behavioural work that does not meet full-dose criteria (e.g. conducted only as homework or in the clinic room, or planned but not completed); and (3) no dose reflected by fewer than six sessions and/or insufficient components to achieve a rating of partial or full dose.

Therapy cases were rated with respect to adherence (full dose vs. partial dose vs. none) by three raters. Raters reviewed the adherence checklists completed by each therapist for each session with each participant. Raters also consulted the additional session notes made by each therapist, again for each session. Inter-rater reliability of the application of adherence criteria was very high, confirming that adherence ratings were very concordant across raters [Krippendorff's alpha = 0.9, bootstrapped 95% confidence interval (CI) 0.87 to 0.98].

The competence of the SRT therapists was recorded using the Cognitive Therapy Rating Scale Revised[45] (CTS-R). Competence was rated through all SRT therapists submitting session audiotapes, which were rated by multiple raters using the CTS-R.

Enhanced standard care

The control comparator was ESC alone. The aim of ESC was to provide the optimal combinations of currently available evidence-based medical, psychological and psychosocial treatments to this group. There was no restriction on access to existing NHS standard treatment for young people with non-psychotic severe and complex mental health problems and social disability. ESC aimed to include provision of short-term individual and family psychological therapies, medication management, and support and monitoring within primary or secondary mental health services. Participants also received a range of education, social, training, vocational and youth work interventions from a variety of statutory and non-statutory service providers, including social services, voluntary agencies, and employment and education providers. ESC also involved a best practice manual (see *Report Supplementary Material 3*) for standard treatment, provided by the trial team to the referrer and usual care provider/case manager at referral and again at the end of the participant's involvement in the study. This manual summarised good practice, including referral to a range of both statutory and third-sector mental health services and medication management, where appropriate. The best practice manual was produced by monitoring and mapping service contacts received across a range of services in the population of interest.

Participants and referrers and/or the usual clinical team, with participant consent, received an assessment summary report from the trial team pertaining to clinical (symptom and neurocognitive) and social problems and circumstances. Assessments identified risks to self or others and these were communicated to the referrer and/or usual care team to facilitate appropriate management. The best practice manual and the approach of the trial team were supported by service user groups and steering groups overseeing youth mental health provision in each region, and delivery was well received by participating services, with referrers keen to involve participants in both treatment and control arms.

Randomisation

Following pretrial assessments, consenting participants were randomised to trial arms stratified by age (16–19, 20–25 years); site (Sussex, East Anglia, Manchester); severity of social disability (low functioning = 16–30 hours of structured activity per week, very low functioning = 0–15 hours of structured activity per week); and whether or not they met symptomatic criteria for ARMS. A remote

randomisation service allocated groups and was co-ordinated by the Norwich Clinical Trials Unit (NCTU). Allocation was by preset lists of permuted blocks with randomly distributed block sizes (agreed with the trial statistician). The lists were generated by the Data Management Team at the NCTU.

The allocation process was web based and managed as part of the trial data management system (TDMS). The allocation sequence was hidden from TDMS users. Once allocated, the details were e-mailed to nominated individuals at the trial site to enable the allocation of treatment to be implemented. The allocation was not revealed to any other users of the database or other individuals.

Blinding

Research assistants collecting baseline and follow-up data were blinded to group allocation. This was successfully maintained in the pilot using a range of procedures, which were subsequently used in the definitive trial.[1] Following allocation to the treatment or control arm, all participants in the study, as well as their care co-ordinator/referrer and clinical team (if applicable), were asked not to reveal to the research assistant (RA) the group to which the participants were randomised. Participants and family members were asked at the beginning of each assessment interview not to disclose the group to which the individual was allocated. Outside the assessments, RAs were shielded from discussion of participants in study forums where the possibility of determining the allocation group of the participants could occur. A system of web-based data entry ensured that RAs did not have access to information in the database that would reveal the allocation group. Data entered into the TDMS by trial therapists that might inadvertently lead to unblinding were hidden from non-trial therapist users.

Reported blind breaks were managed to maintain blind outcome assessments by reallocating 'blind' RAs to collect and score study data, and thus did not bias results. Thirty-one blind breaks occurred during the trial, but all were managed by reallocating the assessment to a blind member of trial staff. Of these blind breaks, 16 were due to the participant or a family member informing the RA of the allocation, 14 were due to referrers or other clinical staff informing the RA of allocation and one was due to a trial staff administrative error.

Patient and public involvement

Patient and public involvement (PPI) activity was led by Dr Rory Byrne. Young people with lived experience of mental health problems and NHS service use were initially recruited from EIP services in Norfolk. These young people were asked to inform the development of the original trial protocol,[1] including advising on the feasibility and acceptability of the SRT intervention and the planned study assessment process.

During the internal pilot, a specific patient group [the PRODIGY Advisory Team (PAT)] was established. The PAT was fully integrated into the development and delivery of the internal pilot. The PAT contributed to the development and revisions of the trial protocol and all participant documentation.[1] Members of the PAT piloted trial assessments using role-play to inform the process of assessment selection and delivery. The PAT also provided consultation promotional materials and trial team training. The PAT improved recruitment to the internal pilot through advising on methods of engaging young people in the trial and in the provision of participant newsletters to facilitate ongoing engagement with the trial. In May 2014, the PAT reviewed the delivery of the internal pilot and contributed to the development of the funding application for the extension phase, most notably in the creation of the lay summary.

The extension phase comprised continued delivery of the trial protocol,[1] as in the internal pilot, with no changes. Therefore, in the extension phase, PPI activity consisted of review of the delivery of the trial protocol by Dr Rory Byrne and Ms Ruth Chandler, lead for PPI for the extension phase sponsor, Sussex Partnership NHS Foundation Trust. Dr Rory Byrne reviewed participant documentation, such as dissemination newsletters. Dr Rory Byrne continues to consult on dissemination activities.

Outcomes

Primary outcome

The primary outcome was time use (hours per week engaged in structured activity) measured at 15 months post randomisation. This assessment was derived from the Office for National Statistics TUS interview,[46] adapted for use with a clinical population.[47] Time use is an important marker of participation in structured activities that are robustly associated with reduced mental health problems and better mental health and well-being;[48,49] thus, time use is a useful measure of the behavioural aspects of social recovery.[47] The TUS is validated for use with young people with mental health problems, is sensitive to discriminating between clinical and non-clinical groups,[47] and shows convergent validity with measures of quality of life and social functioning.[37] Moreover, the derived outcome score is in the easily interpretable metric of weekly hours. Number of hours per week engaged in structured activity includes time spent in both constructive economic activity (e.g. paid and voluntary work, education, child care, housework and chores) and in structured leisure and sports activities. This total was also calculated without child care hours, as child care (especially of a new-born child) considerably inflates time in structured activity, but is an outlying, semirandom event that is unrelated to trial arm and is imbalanced towards female participants. In all relevant outcome models, time use was tested using the total with and without child care hours included.

Secondary outcomes

Further time use outcomes

- Time use[46,47] at the 9-month follow-up point.
- Total hours spent in employment, education and voluntary work since last assessment point, analysed at 9 and 15 months.

Emotional disturbance using self-report questionnaires

- Social anxiety [Social Interaction Anxiety Scale[50] (SIAS) total score].
- Depression (Beck Depression Inventory-II[51] total score).
- Scale for the Assessment of Negative Symptoms[52] (SANS).
- Global Assessment of Functioning[53] (GAF).
- Global Assessment of Symptoms[54] (GAS).
- Social and Occupational Functioning Assessment Scale[55] (SOFAS).

Levels of attenuated psychotic symptoms and associated psychopathology using the Comprehensive Assessment of At-Risk Mental States for psychosis

- Transition to psychosis since last assessment was recorded as a dichotomous variable (transition or no transition).
- Comprehensive Assessment of At-Risk Mental States for psychosis (CAARMS) symptom scores were derived following the procedure used in EDIE-2:[34]
    - A CAARMS symptom severity score (0–144) was derived using the summed product of global severity (0–6) and frequency scores (0–6) across the four positive symptom subscales (unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech). Higher scores reflect more severe symptoms.
    - A CAARMS distress score was created by taking a mean average of subjective distress (0–100) across the four positive symptom subscales.

Change in difficulties experienced by participants in the study using the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders-IV

- Meeting diagnostic criteria for any mood disorders rated since last assessment point.
- Meeting current month diagnostic criteria for up to two anxiety, somatoform or eating disorders for which diagnostic criteria were met at baseline.

Putative mediators

- Acceptance and Avoidance Questionnaire II.[56]
- Meaning in Life Questionnaire.[57]
- Trait Hope Scale.[58]
- Brief Core Schema Scales.[59]
- Schizotypal Symptoms Inventory[60] (SSI) (SSI anomalous experiences, SSI paranoia, SSI social anxiety, and SSI total score).

Putative moderators

- Logical Memory I subtest of the Wechsler Memory Scale, third edition.[61]
- Controlled Oral Word Association Test[62] (COWAT).

Other outcomes

- Alcohol Use Disorders Identification Test[63] (AUDIT) total score.
- Drug Use Disorders Identification Test[64] (DUDIT) total score.
- Beck Hopelessness Scale[65] (BHS) total score.

Health economic outcomes

- Health Service Resource Use Questionnaire.[66]
- EuroQol-5D (EQ-5D) [EuroQol-5 Dimensions, three-level version (EQ-5D-3L)].[67]

All outcomes were assessed at baseline and again at 9, 15 and 24 months post randomisation. The neurocognitive assessments were assessed only at baseline and at 15 months post randomisation. Further information regarding the timing of the assessments is shown in *Appendix 2*.

Participants

Sample size

The target sample size was 270 participants, providing 135 participants in each trial arm. The primary outcome was hours per week in structured activity on the TUS[46,47] at 15 months, which was considered unlikely to follow a normal distribution, but potentially to have a positive skew. It was expected, therefore, that analyses would probably use logarithmically transformed data. The sample size was based on an effect size of 0.4 standard deviations (SDs) being considered a minimum clinically significant benefit. A total of 270 participants would provide > 90% statistical power to detect a 0.4 SD effect size using a two-sided 5% significance level; a total of 200 participants (i.e. accounting for > 25% loss to follow-up) would provide 80% statistical power for the same effect size. A total of 100 participants were recruited in the internal pilot phase (January 2013–February 2014) and 170 further participants were recruited in the definitive extension phase (September 2015–May 2017). The pilot participants were recruited on time and to target. A recruitment extension of 6 months was required to achieve the target of 170 participants for the extension phase. This delayed the planned end date of recruitment from November 2016 to May 2017.

Follow-up assessment for the pilot 100 participants began in September 2013 and finished in March 2016. Follow-up assessment for the extension 170 participants began in June 2016 and finished in June 2019.

Inclusion criteria

- Young people aged 16–25 years with non-psychotic severe and complex mental health problems and showing early signs of persistent social disability.
- Presence of impairment in social and occupational function indicated by patterns of structured and constructive economic activity of < 30 hours per week and a history of social impairment problems lasting for > 6 months.
- Presence of non-psychotic severe and complex mental health problems defined operationally as either of the following:
    - having APS that meet the criteria for ARMS
    - having non-psychotic severe and complex mental health problems which score ≤ 50 on the GAF scale (which indicates the presence of severe symptoms of at least two out of depression, anxiety, substance misuse, behavioural or thinking problems or subthreshold psychosis to the degree that they impair function), with at least moderate symptoms persisting for > 6 months.

Exclusion criteria

- Active positive psychotic symptoms or history of FEP.
- Severe learning disability problems (mild to moderate learning difficulties were not an exclusion criterion).
- Disease or physical problems likely to interfere with ability to take part in interventions and assessments.
- Non-English speaking to the degree that the participant is unable to fully understand and answer assessment questions or give informed consent.

Analytic plan

The analytic plan was detailed in the Statistical Analysis Plan (version 0.2, 4 July 2018) and approved by the Data Monitoring and Ethics Committee (DMEC). The primary analysis compared SRT plus ESC with ESC alone on time use at 15 months post randomisation. The primary analysis was on the intention-to-treat (ITT) principle (i.e. all participants were followed up for data collection irrespective of adherence to treatment and were analysed according to group allocation rather than intervention received). We also completed a per-protocol (PP) analysis of primary and secondary outcomes.

All hypothesis testing was at the two-sided 5% statistical significance level. CIs for parameter estimates were at the corresponding 95% level. Analyses were conducted by the trial statistician blinded to group identity (i.e. 'subgroup' blind).[1] Assuming a normal distribution (potentially of transformed values) for time use, a general linear model was constructed. This model included all stratification variables [i.e. recruiting site (as a random factor), age (16–19 years, 20–25 years), severity of social disability (withdrawn or extremely withdrawn) and meeting symptomatic criteria for an ARMS or not]. Time use at baseline was also included as a covariate. Logical memory at baseline was also included as a prognostic variable for long-term social recovery along with verbal fluency (total score). Treatment arm was included as a fixed effect. Estimation of model parameters was on the basis of 'type III' (or 'adjusted') least squares. The residuals from this model were examined to assess the normal distribution and homoscedastic assumptions. Transformations of the outcome were considered in the case that this assumption did not appear appropriate.

Secondary analyses were conducted in an analogous fashion through a generalised linear model, with an appropriate link and error term depending on the nature of the outcome of interest (e.g. a logistic regression model for binary outcomes). Stratification variables were again included in the model and, where available, the outcome variable at baseline was also included. Treatment group was included as a fixed factor.

The analytic plan included a consideration of the moderation of treatment effect with respect to the following baseline characteristics:

- ARMS[29] status
- low or very low functioning according to structured activity hours per week at baseline[46,47] Logical Memory I (Logical Memory Scaled Total Score[61])
- COWAT[62] total score.

This was to be achieved by using an interaction term (between the putative moderator and treatment arm) to formally assess differences in treatment effect. The sample size calculation did not include reference to hypothesis testing of interaction effects and this analysis was considered exploratory.

Missing data

For both the primary and secondary outcomes, the extent and patterns of missing data were checked and full information maximum likelihood (FIML) methods were used if the degree of missing data was < 50% of those randomised for any given analysis (i.e. when considering both missing outcome and prognostic variables in a model).

Multiple imputation (MI) methods were also used as another solution for missing data and for comparison with the FIML model. Factors to include in the imputation model were all those in the analytical model plus those considered likely to be related to the missing values. Any continuous variable exhibiting a strong asymmetric distribution was transformed to produce symmetry, following recommendations for MI.[68] The imputed analysis was based on 10 imputed data sets. Standard errors for parameter estimates were constructed using Rubin's rules. The analysis using imputed data was a secondary sensitivity analysis with complete-case analysis being the primary analysis.

Full information maximum likelihood and MI methods are based on the assumption that data are missing at random. In the present study, there is clear evidence that there are consistently more missing data in the control arm than in the treatment arm. The level of missingness of data and the bias of missingness of data increases over time. This missingness of data is likely to be due to treatment, as therapy increases the engagement of those with more severe symptoms, who tend to drop out in the control group; therefore, this is likely missing not at random. The level of missingness of data and bias at 15 months was reviewed by the statistical team and, as the total level of missingness of data was < 20% and the bias was present but not extreme, it was agreed that the ITT analysis was the appropriate test of primary and secondary outcomes at that stage. At 24 months, the interpretation of results requires care. The bias assists a conservative assessment of the superiority of SRT and, indeed, may bias in favour of ESC. FIML and MI are reported as supportive analyses but, again, such missing data analyses cannot adjust for bias due to being missing not at random.

Additional analyses

The moderation of treatment effect on the primary outcome, time use at 15 months, was considered with respect to the following baseline characteristics:

- Logical Memory I (Logical Memory Scaled Total Score[61])
- COWAT[62] total score
- at-risk mental state versus not-at-risk mental state from the CAARMS.[29]

This was achieved by using an interaction term (between the putative moderator and treatment arm) to formally assess differences in treatment effect. The sample size calculation did not include reference to hypothesis testing of interaction effects and this analysis is considered exploratory.

Software

The analyses were carried out in SAS® software (version 9.4) (SAS Institute Inc., Cary, NC, USA). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.

Chapter 3 Development and process evaluation

This report has been prepared using CHEERS (Consolidated Health Economic Evaluation Reporting Standards) (see *Report Supplementary Material 4*) and CONSORT (Consolidated Standards of Reporting Trials) (see *Report Supplementary Material 5*) guidance. The completed checklists are provided as supplementary material.

Internal pilot statement

The internal pilot (NIHR reference 10/104/501) was funded in March 2012 and began recruitment in January 2013. The aims of the pilot were to (1) assess recruitment rate, quality of data collection and follow-up, (2) provide a final check on procedures in the protocol and (3) conduct a qualitative substudy to inform the objectives, using a qualitative, service user perspective. The following stop–go criteria were used to determine if it was appropriate for the pilot to be considered an internal pilot and progress to the definitive trial: (1) no necessity for substantive changes to the protocol, (2) recruitment of 80% of the planned total in the first 12 months, (3) retention of participants within the study with baseline and outcome assessments completed for > 80% of participants for the secondary and other outcomes and mediators, and for 90% of participants for the primary outcome, and (4) satisfactory delivery of competent and adherent therapy to > 80% of the treatment group.

The stop–go criteria were all satisfied. No changes to the trial protocol were necessary. The pilot recruitment was on time and to target. Primary and secondary outcome retention was excellent, achieving 92% at both 9- and 15-month assessment points. Primary and secondary outcome retention at the later-added 24-month assessment point necessitated a new consent procedure and a completion rate of 69% was achieved. Of those randomised to SRT ($n = 47$), 41 (87%) were deemed to have received competent and adherent therapy. The pilot DMEC and Trial Steering Committee (TSC) reviewed trial data in 2014 and supported confirmation of the pilot as an internal pilot. These two committees and the PPI representatives (the PAT) reached consensus that no changes to the trial protocol were required. The sponsor also performed a full Good Clinical Practice audit of the trial and concluded that no changes to trial procedures were needed. Additional funding was sought (NIHR reference 10/104/51) for the extension and was awarded in May 2015, with recruitment beginning in September 2015.

Process evaluation

The PRODIGY process evaluation was an evaluation of both the research and the intervention processes undertaken as three substudies, two involving patient participants and one involving SRT therapists, during the initial internal pilot phase. The patient process evaluation was conducted by a subresearch team led by a user researcher (RB) and an independent qualitative researcher (CN), neither of whom were involved in the development of SRT. Both parts of the patient process evaluation (i.e. research and intervention process substudies) were investigated using a qualitative methodology with qualitative interview data collection (see *Report Supplementary Material 3*) and thematic analytic methods.[69] These substudies were published as project outputs.[70,71] The final part of the process evaluation was conducted by a separate subresearch team during the non-pilot extension phase and focused exclusively on SRT therapist experiences of therapy delivery.

Research process evaluation

The research process evaluation was a qualitative exploratory substudy. All participants who had been randomised were invited to participate between April 2013 and mid-June 2013, resulting in a convenience sample of 13 participants.[71] An attempt was made to recruit substudy participants from both trial sites (East Anglia and Manchester) and both trial arms. Participant characteristics are shown in *Table 1*. Interviews were conducted by a user researcher (RB) and a RA between 1 month and 3 months after study randomisation. The interview schedule was semistructured and designed to probe experiences relating to study participation. Data were analysed using an inductive thematic approach[72,73] with a critical realist epistemic stance.[74] Themes are shown in *Table 2*.

The themes focused around key reflections on noteworthy aspects of participating in the PRODIGY trial.[71] First, 'practicalities' reflected the importance of RAs offering flexible research appointments. Flexibility on behalf of the researchers was seen as a manifestation of empathy and a person-centred approach. Second, 'acceptance' emphasised the position of openness from which participants approached their trial participation. Participants appeared to support the process of randomisation as a 'fair' way to allocate the intervention; they also appreciated the scientific importance of the 'control' group or comparator. The assessment process was described as acceptable even if questions were sensitive, again, within the context of a positive rapport with the RA. Third, 'disclosure' was positioned as a useful and therapeutic process within the context of assessment completion with the RA. The extent of their own

TABLE 1 Process evaluation substudy participant characteristics

	Characteristic, *n* (%)											
	Age (years)		Sex		Allocation arm		Site		Social disability		At-risk mental states	
Substudy	16–19	20–25	Male	Female	SRT + ESC	ESC	Manchester	East Anglia	Very low	Low	At risk	Not at risk
Research process: substudy 1[71]	7 (54)	6 (46)	9 (69)	4 (31)	6 (46)	7 (54)	7 (54)	6 (46)	11 (85)	2 (15)	4 (31)	9 (69)
Intervention process: substudy 2[70]	11 (65)	6 (35)	8 (47)	9 (53)	8 (47)	9 (53)	8 (47)	9 (53)	11 (65)	6 (35)	6 (35)	11 (65)

TABLE 2 Qualitative themes derived from process evaluation substudies

Study	Theme application	Themes				
Research process: substudy 1[71]	Across participants	Practicalities	Acceptance	Disclosure	Altruism	Engagement
Intervention process: substudy 2[70]	Across participants	'It's just the speaking to someone': the value of talking	'Just do it': the importance of activity	Motivation to change		
	SRT + ESC	'She understood me on a personal level': the therapeutic relationship	Flexibility	'It's given me tools': the CBT toolkit	No pain, no gain: SRT as difficult	
	ESC alone	Allocation ambivalence	No treatment, as usual	'I was the one who had to do everything to help overcome it'		

disclosure, and the positive experience thereof, seemed to be a surprise for many participants. Fourth, 'altruism' appeared to be a key reason for participants wanting to be involved in the trial. This related to trial involvement in general and, more specifically, to participants being in support of the randomised controlled nature of the trial. A minority of participants appeared not to have a good understanding of randomisation. Finally, 'engagement' was a key theme that reflected the sense of being involved in the trial as a positive experience. Despite the main focus of the substudy being the research process, participants spoke of their thoughts and experiences in relation to the SRT intervention. Engagement in SRT was seen to be helpful; participants highlighted the benefits of understanding their experiences and how things could change for the better. Nevertheless, participants also described SRT as challenging.

Intervention process evaluation

The focus of the intervention process evaluation was on both arms of the trial (i.e. SRT plus ESC, and ESC alone). Participants were purposively sampled from those involved in the trial (pilot 100 participants only) aiming to balance across sex, study site (East Anglia and Manchester), allocation and baseline ARMS status. Attempts were also made to involve participants reflecting maximum variation in age and prior service use, and to include looked-after children.[70] Nineteen people participated, and their characteristics are shown in *Table 1*.

Participants were interviewed by one of two researchers using a semistructured interview schedule. Questions focused on experience of psychological difficulties and previous service use, experience of trial participation and interventions received, and perceived outcomes and thoughts about future well-being. Data were analysed with an inductive thematic analysis approach[69,72] taking a critical realist epistemic stance. Themes are shown in *Table 2*.

There were three themes common to the accounts of all participants.[70] First, "'It's just the speaking to someone': the value of talking" reflected participants in both arms perceiving there to be a therapeutic value in talking to someone (RA or therapist) during their trial involvement. Many participants felt that they had avoided or not had the opportunity to do so before their trial involvement. Subthemes reflected that talking to someone helped in two main ways: 'it's not boiled up in me no more' and 'it helped me recognise the things that I wanted to change'. Second, "'Just do it': the importance of activity" reflected the sense of importance placed on meaningful activity by participants in both trial arms. For SRT plus ESC participants, doing these activities reflected an important part of the intervention. Yet for ESC-alone participants, increasing their occupational activity also seemed important, and several participants described making clear efforts to increase their activity levels. Finally, 'motivation to change' reflected a sense that determination to make positive changes in their lives was a key feature across the accounts of all participants.

There were four themes corresponding to participant experiences of the SRT intervention.[70] First, "'She understood me on a personal level': the therapeutic relationship" emphasised the centrality of the relationship with the SRT therapist to the participant's experience of SRT. Participants emphasised the informal yet boundaried relationships developed with SRT therapists, which produced a sense of collaborative engagement. Second, the 'flexibility' theme reflected participant appreciation for the flexible way in which the intervention was delivered, for example with respect to timing and location. Third, in "'It's given me tools': the CBT toolkit" participants spoke of how SRT equipped them with tools for managing their own distress and increasing their activity levels. Commonly described 'tools' included behavioural activation and behavioural experiments. Most participants felt that they could use the tools they had gained to their benefit beyond the intervention, although one participant felt that the intervention period was too short to allow them to use the same techniques independently. Finally, 'No pain, no gain: SRT as difficult' reflected that participants experienced the SRT intervention as challenging and even at times painful or overwhelming. Participants tended to emphasise that the 'pain' was worth it as they needed to push themselves to complete challenging exercises in order to improve their situations.

There were three themes corresponding to the experience of treatment as usual (i.e. ESC) only.[70] First, most participants expressed 'allocation ambivalence' and did not seem to hold negative views about having been randomised to ESC. Some expressed relief at not having to attend therapy, which they appeared to feel would have been anxiety-provoking. However, two participants did express negative views. Second, the theme 'No treatment, as usual' spoke to the experience of young people in the ESC-alone arm of the trial as reflecting an absence of care and support provision. Only two participants reported having received specialist mental health care since their involvement in the trial. Some participants did report support from their general practitioner (GP), although they were not particularly satisfied with the nature of this support. Finally, 'I was the one who had to do everything to help overcome it' reflected ESC-alone participants' sense that they had to manage their mental health independently, in the context of not being offered SRT and the perceived lack of treatment offered by standard mental health services. Some participants did emphasise that there had been considerable improvement in their mental health despite feeling unsupported by any services, conveying a sense of pride and achievement in improving without this additional support.

Therapist experience process evaluation

The focus of the therapist experience process evaluation was to explore therapist experiences of delivering SRT, with a particular focus on therapist hopefulness in the face of engaging with patients with complex presentations. All SRT therapists involved in therapy delivery in the extension phase of the trial, including two therapists who had also been involved in therapy delivery in the internal pilot, were invited to participate. Information about participation was shared verbally and using a PIS (see *Report Supplementary Material 1*). Ten SRT therapists participated in a semistructured individual interview following the provision of consent using an informed consent form (see *Report Supplementary Material 2*). The interview guide focused on asking therapists to reflect on their experiences of delivering SRT, including experiences where therapy had gone 'well' and experiences where it had not gone 'well'. Therapists were also asked about their experiences of informal and formal support and supervision. Data were analysed using interpretative phenomenological analysis.[75] Coding and analysis were performed by a SRT therapist experienced in SRT delivery but not involved in the inception or design of SRT and by a non-therapist researcher.

The finding of the therapy process evaluation was that SRT therapists emphasised the importance of working with this complex client group. In standard services, therapists reported that these young people would typically not be seen, because the typically protracted period needed to engage these young people is usually not possible within the services' policies and practices. SRT therapists reported that, with this complex group, understanding and formulating treatment ambivalence and disengagement was essential, as was the pursuit of meaningful connection with these young people. SRT therapists also spoke of the difficulty of finding and sustaining their own hopefulness in the face of participants' sense of ambivalence, hopelessness and 'stuckness'. Sources of hope and scaffolds for its maintenance included access to expert and hopeful supervision, and opportunities to engage in peer supervision with other SRT therapists.

Process evaluation limitations and conclusions

The key limitations of the process evaluation substudies are that, because of the nature of the convenience sampling methods, the conclusions cannot be said to be generalisable to the whole trial sample or population beyond the trial. Nevertheless, the epistemic stance and qualitative methodologies taken were such that we sought not generalisability, but rather the unique experiences of individual participants of interest. Despite this the findings do show consistency with the wider literature, for example a previous study involving young people with ARMS.[76] Further limitations of the process evaluation substudies include the apparent weighting of the intervention arm participants towards those who had engaged with the therapy. Only one participant was included who had not received a 'dose' of the intervention. Although the majority of participants in the trial did receive a dose, those who did not are an under-represented group and their experiences are particularly important in understanding both research and therapy processes.

Key conclusions of the process evaluation centred around the apparent value of having someone with whom to talk and reflect on mental health and well-being. This value was identified for both the research assessments and SRT. With respect to contact with RAs, the perceived value of the research assessment process seems to reflect the notion of therapeutic assessment[77] (i.e. that assessment alone can have a therapeutic effect on patients). In the first substudy, all but two participants indicated at least some degree of past mental health service involvement, ranging from CAMHS or youth mental health services to school, university, private or third-sector counselling. Nevertheless, these participants still appeared to experience their trial involvement as reflecting a novel sense of 'opening up'. This appears to reflect the particularly in-depth nature of the research assessments and also the flexible, engaging and skilled nature of RAs' interactions with trial participants. It is also notable that in both substudies[70,71] SRT participants emphasised the difficult and challenging nature of the intervention.

Chapter 4 Results

Participant flow

Participant flow through the trial is depicted in *Figure 1*.

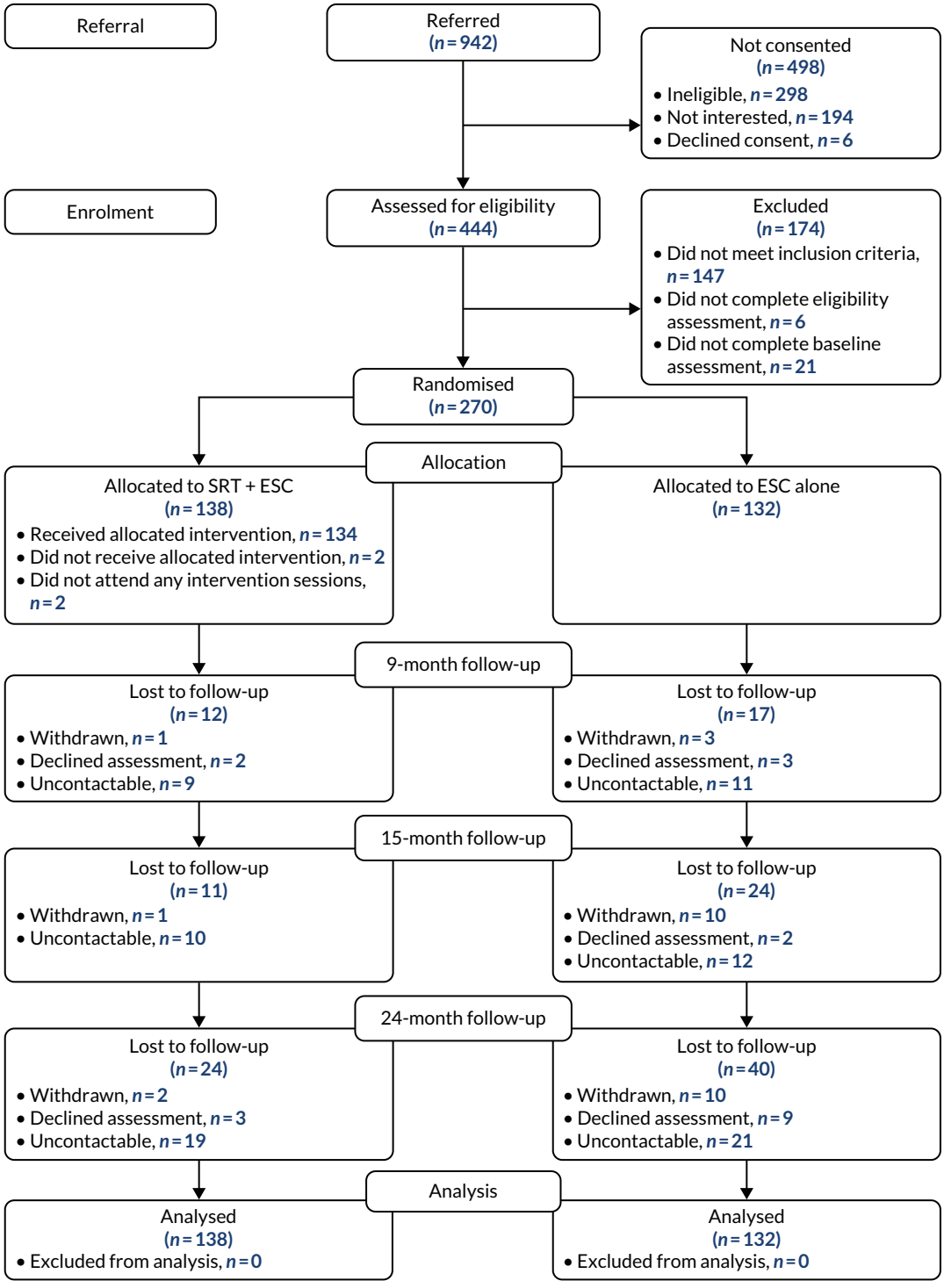

FIGURE 1 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Participant non-entry

As shown in *Table 3*, the majority of participants who were ineligible (1) did not meet entry criteria regarding no history of or current active psychosis evidenced by symptoms and/or prescription of threshold dosage of antipsychotic medication, (2) had insufficient social impairment and/or (3) were not eligible for unknown reasons. The third group included early referrals from clinicians of potential participants who did not reach formal eligibility assessment. As shown in *Table 4*, the majority of participants who declined to participate for lack of interest did not give further reasons for their decision or were categorised as not interested because they and/or their referrers were not contactable (disengaged).

Characteristics of randomised participants

Table 5 provides baseline demographic characteristics of the sample by trial arm conditions and as per the ITT and PP analyses. The aim was to recruit a sample of withdrawn young people with low activity and comorbid complex severe mental illness. There was little difference between the two groups, with both groups showing a majority of participants aged 16–19 years, with a mean age around aged 20 years, of white ethnicity, who were single, unemployed, heterosexual and living in rented accommodation. The ESC sample is evenly balanced between sexes, although there was a predominance of male participants in the SRT group.

Of note is the severity of social disability, and psychopathology anxiety and depression present in the sample at baseline. Around half of the participants ($n = 133$) met the criteria for ARMS. One hundred and fourteen (86%) of the 133 participants with ARMS were categorised as experiencing APS, 11 (8.3%) were categorised as experiencing APS and vulnerability, four (3.0%) were categorised as experiencing vulnerability, three (2.3%) were categorised as experiencing APS and brief limited intermittent psychotic

TABLE 3 Reasons for ineligibility

Reason[a]	Participants (*n*)
Age < 16 years or > 25 years	6
+ Severe learning difficulties	1
Historical or active psychotic symptoms or first episode (or taking antipsychotics at above therapeutic dose)	63
+ Social impairment insufficient[b]	6
Severe learning difficulties	3
Disease or physical problems likely to interfere with ability to take part	4
Non-English speaking	0
Social impairment insufficient[b]	76
Mental health problems insufficient	32
+ Social impairment insufficient[b]	1
Out of area	11
Risk/safety concerns	9
Re-referral of young person who had already participated	3
Reason for unsuitability unknown	91

a Participants may have multiple reasons for ineligibility.
b Structured activity > 30 hours per week or social disability lasting < 6 months.

TABLE 4 Reasons for declining participation

Reason[a]	Participants (*n*)
Not interested (detail unknown)	91
Not help-seeking	19
Not interested in research participation	10
+ Not interested in SRT	9
+ Project too much commitment	3
+ Not interested in SRT, not help-seeking	3
Not interested in SRT	2
Project too much commitment	8
Unable/unwilling to engage due to mental health problem(s)	7
Young person disengaged from referrer	54
Young person disengaged from the PRODIGY trial	64
Referrer disengaged from the PRODIGY trial	70
Recruitment ended	4

a Participants may have multiple reasons for non-participation.

TABLE 5 Baseline characteristics by allocation arm

	Analysis		
	ITT		PP
Characteristic	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 91)
Age group (years)*, n *(%)			
16–19	79 (57)	75 (57)	51 (56)
20–25	59 (43)	57 (43)	40 (44)
Age (years)			
Mean (SD)	20.1 (2.5)	20.0 (2.7)	20.1 (2.4)
Missing, *n*	6	5	2
Sex*, n *(%)			
Female	54 (39)	66 (50)	34 (37)
Male	84 (61)	66 (50)	57 (63)
Ethnicity*, n *(%)			
White	127 (92)	114 (86)	83 (91)
Non-white	11 (8.0)	18 (14)	8 (8.8)
Marital status*, n *(%)			
Partner	18 (13)	17 (13)	9 (9.9)
Separated	2 (1.5)	0	2 (2.2)
Single	118 (86)	115 (87)	80 (88)

continued

TABLE 5 Baseline characteristics by allocation arm (*continued*)

Characteristic	Analysis		
	ITT		PP
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 91)
***Employment status*, n (%)**			
Paid work	5 (3.6)	6 (4.6)	3 (3.3)
Voluntary work	3 (2.2)	4 (3.0)	3 (3.3)
Student	34 (25)	31 (24)	22 (24)
Unemployed	95 (69)	91 (69)	62 (69)
Missing, *n*	1	0	1
***Sexual orientation*, n (%)**			
Heterosexual	98 (74)	107 (82)	64 (74)
Homosexual	6 (4.5)	6 (4.6)	3 (3.5)
Bisexual	16 (12.1)	13 (9.9)	9 (10.5)
Unsure	6 (4.5)	1 (0.8)	5 (5.8)
Other	6 (4.5)	4 (3.1)	5 (5.8)
Missing, *n*	6	1	5
***Accommodation*, n (%)**			
Accommodation with support	8 (5.9)	4 (3.0)	4 (4.5)
Homeless/temporary accommodation	5 (3.7)	7 (5.3)	2 (2.2)
Mobile accommodation	0	1 (0.8)	0
Owner occupied	48 (36)	41 (31)	32 (36)
Rented (local authority/housing association)	45 (33)	55 (42)	27 (30)
Rented (private)	29 (22)	24 (18)	24 (27)
Missing, *n*	3	0	2
***Social functioning*, n (%)**			
Low functioning	40 (29.0)	40 (30)	21 (23)
Very low functioning	98 (71)	92 (70)	70 (77)
***Mental state*, n (%)**			
At risk	69 (50)	64 (49)	49 (54)
Not at risk	69 (50)	68 (52)	42 (46)

symptoms and one (0.8%) was categorised as experiencing brief limited intermittent psychotic symptoms. Around two-thirds of the sample entered the trial with very low functioning according to stratification. The mean structured activity level was around 11 hours, which, when compared with > 64 hours in an age-matched non-clinical sample, suggested extreme withdrawal.[47] Levels of social disability were in the severe range and > 95% of participants were unemployed. Functional status according to GAF and SOFAS similarly suggested severe functional disability.[53,55] Levels of global symptoms, depression, social anxiety and hopelessness were in the severe range,[50,51,54,78] with comorbidity in the majority of cases. Alcohol and drug disorders, aggression and suicidality were also severe and prevalent.[29,63,64]

Baseline scores for the outcome measures were fairly similar across both groups (see *Table 6*). The intervention group reported slightly greater social anxiety (SIAS) and slightly lower functioning (SOFAS) at baseline. The average scores for the CAARMS interview variables at baseline were fairly similar between the control and the intervention groups. The symptom severity and average distress scores were very similar; however, the intervention group showed a slightly lower aggression severity score and a slightly higher suicidality severity score. These results are tabulated in *Table 7*. The diagnostic characteristics of both groups (*Tables 8* and *9*) were similar at baseline, although ESC-alone participants appeared to be slightly more likely to have current panic disorder or panic with agoraphobia, and slightly less likely to report a current major depressive episode. Scores on 'other' outcomes at baseline were similar across groups, although the ESC-alone arm scored slightly lower for hopelessness (*Table 10*).

TABLE 6 Outcomes at baseline

	Population		
	ITT, mean (SD)		PP, mean (SD)
Outcome	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 91)
Primary outcome			
Structured activity (hours per week)	11.3 (8.0)	11.3 (8.6)	9.8 (7.4)
Missing, *n*	0	0	0
Structured activity (minus child care) (hours per week)	11.0 (7.8)	11.2 (8.6)	9.7 (7.3)
Missing, *n*	0	0	0
Secondary time use outcome			
Constructive economic activity (hours per week)	8.6 (7.1)	8.1 (7.0)	7.3 (6.4)
Missing, *n*	0	0	0
Secondary emotional disturbance outcomes			
SIAS	52.1 (14.1)	48.1 (16.1)	53.9 (12.6)
Missing, *n*	3	7	3
BDI-II	30.4 (12.8)	30.3 (12.4)	30.3 (11.8)
Missing, *n*	4	5	4
GAF	37.9 (5.6)	38.2 (5.5)	37.8 (4.6)
Missing, *n*	0	0	0
GAS	43.1 (7.3)	43.2 (7.5)	43.5 (7.0)
Missing, *n*	0	0	0
SOFAS	41.6 (7.6)	43.3 (7.0)	40.5 (6.8)
Missing, *n*	0	0	0

BDI-II, Beck Depression Inventory-II.

Notes
SIAS is a total score on 20 items, each scored from 0 to 4, with higher scores reflecting greater symptomatic severity. A total score ≥ 43 reflects social phobia or social anxiety disorder. The Beck Depression Inventory-II is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater symptomatic severity. A total score ≥ 29 reflects severe depression. GAF is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in symptomatic and functional problems. GAS is an observer-rated score from 0 to 100, with lower scores reflecting greater symptom severity. SOFAS is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in functional problems.

TABLE 7 Comprehensive Assessment of ARMS severity and distress secondary outcomes at baseline

Outcome	Allocation arm	
	SRT + ESC, mean (SD) (*N* = 138)	ESC alone, mean (SD) (*N* = 132)
CAARMS symptom severity score	26.2 (16.5)	26.1 (15.9)
Missing, *n*	1	2
CAARMS average distress score	52.5 (27.0)	52.1 (23.1)
Missing, *n*	6	6
CAARMS aggression severity score	6.3 (5.4)	7.7 (6.0)
Missing, *n*	5	1
CAARMS suicidality severity score	6.7 (6.5)	5.9 (6.4)
Missing, *n*	7	1

The CAARMS symptom severity reflects the product of global severity (scored 0–6) and frequency (scored 0–6) for four positive symptom subscales. CAARMS distress reflects the average distress score (scored 0–100) for four positive symptom subscales. CAARMS aggression and suicidality severity scores reflect the respective products of global severity (scored 0–6) and frequency scores (scored 0–6). Higher scores reflect more severe symptoms.

TABLE 8 Secondary outcomes: structured clinical interview diagnoses (1) mood prevalence at baseline

Outcome	Allocation arm, *n* (%)	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)
Current major depressive episode	72 (52.2)	65 (49.2)
Past major depressive episode	33 (23.9)	41 (31.1)
Current mania	1 (0.7)	1 (0.8)
Past mania	2 (1.5)	5 (3.8)
Current hypomania	5 (3.6)	2 (1.5)
Past hypomania	2 (1.5)	1 (0.8)
Dysthymia	16 (11.6)	15 (11.4)
Bipolar at risk	25 (18.1)	14 (10.6)
Bipolar I	2 (1.5)	5 (3.8)
Bipolar II	4 (2.9)	1 (0.8)
Major depressive disorder	95 (68.8)	93 (70.5)

Rates of retention

Table 11 depicts the proportion of participants assessed at follow-up in each of the three trial sites. Proportions of follow-up are broadly similar. The higher rate of 24-month follow-up in the Sussex site reflects the fact that this site participated in the extension phase only and, thus, all participants consented to this follow-up at the outset.

TABLE 9 Structured clinical interview diagnoses (2) anxiety, eating and somatoform prevalence at baseline

	Allocation arm, *n* (%)	
Outcome	**SRT + ESC (*N* = 138)**	**ESC alone (*N* = 132)**
Panic disorder[a]	6 (4.4)	6 (4.6)
Panic disorder with agoraphobia	18 (13)	25 (19)
Agoraphobia without panic	21 (15)	31 (24)
Social phobia	62 (45)	54 (41)
Specific phobia	10 (7.3)	4 (3.0)
OCD	12 (8.7)	11 (8.3)
PTSD	14 (10)	16 (12)
GAD	36 (26)	44 (33)
Hypochondriasis	4 (2.9)	3 (2.3)
Body dysmorphic disorder	14 (10)	10 (7.6)
Anorexia nervosa	1 (0.7)	1 (0.8)
Bulimia nervosa	1 (0.7)	0 (0.0)
Binge-eating disorder	2 (1.5)	1 (0.8)
Anxiety disorder NOS	4 (2.9)	3 (2.3)

GAD, generalised anxiety disorder; NOS, not otherwise specialised; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder.
a This variable has one missing value at baseline.

TABLE 10 Other outcomes at baseline

	Analysis		
	ITT, mean (SD)		PP, mean (SD)
Outcome	**SRT + ESC (*N* = 138)**	**ESC alone (*N* = 132)**	**SRT + ESC (*N* = 91)**
BHS	13.4 (5.8)	12.7 (5.2)	13.7 (5.6)
Missing, *n*	9	10	7
AUDIT	5.0 (6.3)	5.2 (6.3)	4.3 (5.6)
Missing, *n*	7	2	2
DUDIT	3.6 (7.2)	3.9 (7.8)	3.2 (7.1)
Missing, *n*	2	1	1

The BHS is a total score on 20 items, each scored 0 or 1, with higher scores reflecting greater hopelessness. A total score of 9–14 reflects moderate hopelessness. AUDIT is a total score on 10 items, each scored from 0 to 4, with higher scores reflecting greater alcohol use. A total score of 1–7 indicates low risk, with a score ≥ 8 reflecting hazardous drinking and ≥ 15 reflecting potential alcohol dependence. DUDIT is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater drug use. There are no published clinically relevant DUDIT thresholds.

Intervention results

Description of enhanced standard care

Data regarding participant health and support service use were collected at each assessment point. The reporting period at baseline covered the 6 months prior to the assessment date. At each follow-up assessment, the reporting period covered the time since the previous assessment point.

TABLE 11 Summary of follow-up by site

Time point	Site	Proportion of participants assessed at follow-up, *n* (%)			
		Completed	Uncontactable	Declined	Withdrawn
9	Sussex	53 (93)	2 (3.5)	0 (0.0)	2 (3.5)
	East Anglia	102 (94)	5 (4.6)	1 (0.9)	0 (0.0)
	Manchester	86 (83)	13 (13)	4 (3.8)	1 (1.0)
	Total	241 (89)	20 (7.4)	5 (1.9)	4 (1.5)
15	Sussex	50 (88)	4 (7.0)	0 (0.0)	3 (5.3)
	East Anglia	98 (90)	4 (3.7)	1 (0.9)	6 (5.5)
	Manchester	87 (84)	14 (14)	1 (1.0)	2 (1.9)
	Total	235 (87)	22 (8.1)	2 (0.7)	11 (4.1)
24	Sussex	49 (86)	4 (7.0)	1 (1.8)	3 (5.3)
	East Anglia	84 (77)	11 (10)	8 (7.3)	6 (5.5)
	Manchester	73 (70)	25 (24)	3 (2.9)	3 (2.9)
	Total	206 (76)	40 (15)	12 (4.4)	12 (4.4)

Mental health service use was recorded as the number of contacts (*Table 12*). Overall, high incidence of mental health service use is noted and, in most cases, incidence is highest in the ESC-alone arm. Of particular note is the especially large number of individuals in the ESC-alone arm who received psychological therapies between baseline and the 9-month assessment point: 44% of participants received, on average, almost nine therapy sessions. Furthermore, the majority of participants in both arms reported 6–8 sessions of psychological therapy in the 9-month period leading up to trial entry (see *Table 12*). The majority of participants in both arms reported GP contacts at baseline and throughout the trial, and the majority of participants in both arms were taking antidepressant medication (see *Table 12*). A sizeable minority of participants also had case management, psychiatrist input and additional medication; case management was higher for SRT plus ESC participants across the trial, and psychiatrist input and additional medication were more frequent for ESC-alone participants.

It is also noteworthy that a higher proportion of participants in the SRT plus ESC arm (12%) than in the ESC-alone arm (4%) were taking antipsychotic medication at trial entry (see *Table 12*). The slightly higher rate in the SRT plus ESC arm was notable across the follow-up points. In addition, the rate of psychiatric admission (8% vs. 3%) and length of stay (11.6 vs. 1.7 days) were slightly higher in the SRT plus ESC arm than in the ESC-alone arm at baseline, and this pattern continued across follow-ups. A higher rate of accident and emergency visits was reported in the SRT plus ESC arm than in the ESC-alone arm at baseline (15% vs. 11%); however, this pattern reversed across the follow-up periods (see *Table 12*).

With respect to 'packages' of care (*Table 13*), participants allocated to SRT plus ESC (38% at 9 months and 54% at 15 months) were more likely than those assigned to ESC alone (30% at 9 months and 42% at 15 months) to have no NHS mental health service provision. Where provision did occur, the 'packages' of care appeared similar across both trial arms during the trial [other than the ESC-alone arm being more likely than the SRT plus ESC arm to have therapy during the 9-month intervention window only (21% vs. 9%)].

Personal and support services were recorded in terms of the number of participants accessing such services and the duration of support, in hours (*Table 14*). It is notable that one-quarter to one-third of participants in both arms reported multiple hours of employment support across the trial period. Large SDs for the mean average values (see *Table 14*) suggest that the number of hours of personal

TABLE 12 Frequency of health service use per allocation arm

Resource	Time point, *n* (%)/mean (SD)							
	Baseline		9 months		15 months		24 months	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 108/132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 100/132)	SRT + ESC (*N* = 107/138)	ESC alone (*N* = 83/132)
GP								
Presence	94 (68%)	105 (80%)	92 (74%)	69 (64%)	87 (70%)	68 (68%)	79 (74%)	55 (66%)
Contacts	5.4 (7.7)	4.1 (3.5)	4.9 (5.8)	5.3 (4.4)	3.0 (3.5)	4.2 (3.7)	4.6 (7.1)	5.3 (6.1)
Psychiatrist								
Presence	27 (20%)	37 (28%)	22 (18%)	23 (21%)	13 (10%)	18 (18%)	16 (15%)	14 (17%)
Contacts	2.9 (3.6)	2.85 (3.0)	2.0 (1.5)	2.6 (2.2)	3.2 (3.2)	1.4 (0.51)	1.9 (1.4)	2.6 (2.9)
Psychological therapies[a]								
Presence	71 (51%)	73 (55%)	33 (27%)	47 (44%)	26 (21%)	25 (25%)	30 (28%)	26 (31%)
Contacts	8.0 (9.1)	6.3 (5.6)	11.8 (19.8)	8.9 (6.3)	6.9 (10.1)	6.8 (11.4)	10.3 (11.9)	8.8 (10.9)
Case management[b]								
Presence	54 (39%)	75 (57%)	58 (47%)	41 (38%)	45 (36%)	39 (39%)	33 (31%)	31 (37%)
Contacts	10.3 (14.4)	9.7 (17.5)	11.5 (13.7)	11.3 (13.9)	9.02 (11.3)	10.8 (11.4)	10.6 (12.1)	10.0 (13.7)
Medication								
Antidepressant	78 (57%)	78 (59%)	71 (57%)	59 (55%)	61 (49%)	49 (49%)	60 (56%)	41 (49%)
Antipsychotic	16 (12%)	5 (3.8%)	14 (11%)	3 (2.8%)	13 (10%)	4 (4.00%)	12 (11%)	2 (2.4%)
Other	24 (17%)	35 (27%)	18 (15%)	18 (17%)	20 (16%)	22 (22%)	26 (24%)	17 (20%)
Additional anxiolytic	12 (8.7%)	19 (14%)	10 (8.06%)	15 (14%)	11 (8.9%)	12 (12%)	16 (15%)	10 (12%)
Benzodiazepines	7 (5.07%)	7 (5.3%)	7 (5.7%)	4 (3.7%)	7 (5.7%)	4 (4.00%)	4 (3.7%)	2 (2.4%)
Mood stabilisers	0 (0.0%)	3 (2.3%)	1 (0.81%)	2 (1.9%)	1 (0.81%)	3 (3.00%)	1 (0.93%)	2 (2.4%)
Stimulants[c]	5 (3.6%)	11 (8.3%)	5 (4.03%)	5 (4.6%)	4 (3.2%)	5 (5.00%)	5 (4.7%)	3 (3.6%)

continued

TABLE 12 Frequency of health service use per allocation arm (*continued*)

Resource	Time point, *n* (%)/mean (SD)							
	Baseline		9 months		15 months		24 months	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 108/132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 100/132)	SRT + ESC (*N* = 107/138)	ESC alone (*N* = 83/132)
Psychiatric admissions[d]								
Number of people	11 (7.9%)	4 (3.03%)	5 (4.03%)	1 (0.93%)	6 (4.8%)	2 (2.00%)	7 (6.5%)	3 (3.6%)
Number of visits	1.6 (1.2)	1.00 (0.00)	1.8 (1.8)	4.00 (–)	1.3 (0.82)	3.00 (2.8)	1.7 (1.1)	1.00 (0.00)
Total days	11.6 (26.1)	1.7 (1.2)	5.00 (4.3)	6.00 (0.00)	23.2 (39.4)	6.00 (4.2)	10.4 (14.7)	1.00 (0.00)
Accident and emergency contacts (non-admission)								
Number of people	21 (15%)	14 (11%)	15 (12%)	18 (17%)	14 (11%)	18 (18%)	16 (15%)	13 (16%)

a Including with a clinical psychologist, psychological therapist or counsellor.
b Including case managers, care co-ordinators, and key workers of various professional backgrounds such as mental health nursing, occupational therapy, and social work.
c Prescribed in the context of attention deficit and hyperactivity disorder.
d Includes all admissions to psychiatric and psychiatric respite hospitals, and admissions to accident and emergency that are psychiatric in nature.

TABLE 13 Mental health service 'packages' of care per allocation arm

Care 'package'	Time point, *n* (%)							
	Baseline		9 months		15 months		24 months	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 108/132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 100/132)	SRT + ESC (*N* = 107/138)	ESC alone (*N* = 83/132)
No NHS mental health provision	18 (13)	23 (17)	47 (38)	32 (30)	66 (54)	42 (42)	52 (49)	38 (46)
Care co-ordinator/keyworker only	29 (21)	23 (17)	30 (24)	19 (18)	25 (20)	21 (21)	16 (15)	13 (16)
Psychological therapy only	33 (24)	40 (30)	11 (8.9)	23 (21)	11 (8.9)	12 (12)	17 (16)	9 (11)
Psychological therapy plus care co-ordinator/keyworker	21 (15)	19 (14)	14 (11)	11 (10)	8 (6.5)	7 (7.00)	7 (6.5)	7 (8.4)
Psychiatrist only	7 (5.07)	6 (4.5)	6 (4.8)	6 (5.6)	1 (0.81)	3 (3.00)	5 (4.7)	2 (2.4)
Psychological therapy plus care co-ordinator/keyworker plus psychiatrist	11 (7.9)	6 (4.5)	6 (4.8)	7 (6.5)	6 (4.9)	2 (2.00)	5 (4.7)	6 (7.2)
Care co-ordinator/keyworker plus psychiatrist	13 (9.4)	8 (6.06)	8 (6.45)	4 (3.7)	6 (4.9)	9 (9.00)	6 (5.6)	3 (3.6)
Psychological therapy plus psychiatrist	6 (4.4)	7 (5.3)	2 (1.61)	6 (4.8)	0 (0.0)	4 (4.00)	0 (0.0)	3 (3.6)

TABLE 14 Personal and support service use by allocation arm

Service use	Time point, *n* (%)/mean (SD)							
	Baseline		9 months		15 months		24 months	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 108/132)	SRT + ESC (*N* = 124/138)	ESC alone (*N* = 100/132)	SRT + ESC (*N* = 107/138)	ESC alone (*N* = 83/132)
Employment support								
Presence	33 (24%)	36 (27%)	42 (34%)	43 (34%)	39 (31%)	27 (27%)	32 (30%)	25 (30%)
Duration (hours)	10.07 (25.2)	5.00 (7.01)	8.5 (13.3)	9.0 (19.3)	8.4 (17.6)	11.5 (17.9)	56.1 (173.0)	7.9 (10.8)
Youth services								
Presence	9 (6.5%)	15 (11%)	16 (13%)	12 (11%)	5 (4.03%)	4 (4.00%)	4 (3.7%)	5 (6.02%)
Duration (hours)	13.2 (24.2)	6.3 (4.4)	8.2 (9.8)	36.7 (97.4)	18.2 (20.8)	52.2 (43.7)	27.1 (51.9)	16.3 (11.6)
Statutory services								
Presence	17 (12%)	19 (14%)	9 (7.3%)	9 (8.3%)	4 (3.2%)	4 (4.00%)	5 (4.7%)	4 (4.8%)
Duration (hours)	4.6 (6.2)	5.1 (6.6)	2.1 (2.3)	21.8 (52.32)	5.00 (1.7)	161.5 (320.1)	27.1 (52.0)	61.5 (119.0)
Telephone support								
Presence	14 (10%)	11 (8%)	7 (6%)	10 (9%)	8 (7%)	5 (5%)	8 (8%)	8 (10%)
Duration (hours)	4.7 (6.3)	1.3 (1.8)	6.9 (8.8)	35.1 (100.1)	0.81 (0.5)	1.1 (0.9)	2.0 (2.2)	1.7 (1.6)
Social support groups								
Presence	4 (2.9%)	4 (3.03%)	8 (6.5%)	7 (6.5%)	6 (4.8%)	4 (4.00%)	3 (2.8%)	4 (4.8%)
Duration (hours)	27.3 (27.8)	26.7 (39.1)	22.8 (18.2)	33.5 (58.5)	9.8 (8.1)	43.5 (58.7)	5.3 (2.3)	66.3 (53.6)
Housing services and support								
Presence	14 (10%)	15 (11%)	17 (14%)	10 (9%)	11 (8.9%)	6 (6.00%)	7 (6.5%)	8 (9.6%)
Duration (hours)	4.6 (6.0)	25.1 (66.5)	10.7 (19.1)	8.1 (11.6)	10.5 (12.7)	3.00 (1.4)	15.8 (12.3)	2.5 (2.4)
Financial services and support								
Presence	11 (8.00%)	8 (6.06%)	12 (9.6%)	11 (10%)	7 (5.7%)	8 (8.00%)	6 (5.6%)	8 (9.6%)
Duration (hours)	1.9 (1.9)	1.6 (1.1)	3.1 (4.1)	21.8 (52.3)	2.7 (4.1)	2.01 (2.2)	2.5 (1.9)	0.95 (0.96)
Educational services and support								
Presence	6 (4.4%)	11 (8.3%)	16 (12%)	14 (13%)	12 (9.7%)	4 (4.00%)	4 (3.7%)	3 (3.6%)
Duration (hours)	6.1 (1.5)	22.1 (35.6)	68.1 (121.8)	43.7 (113.9)	18.7 (25.7)	3.8 (1.8)	2.5 (2.1)	158.7 (267.9)

and social support that individuals receive is extremely variable, with some individuals having received very high amounts of personal and social support over the reporting periods, especially with respect to youth and statutory service provision and social support group attendance.

Social recovery therapy adherence and competence

Adherence

The number of SRT sessions received by participants ranged from 0–33, with a mean of 16.8 sessions (SD = 7.9 sessions). Of the 138 participants who were randomised to receive SRT, 91 (68%) received the full dose, 23 (17%) received a partial dose and 24 (18%) received no dose. Thus, adherence was reached for 86% of participants in total ($n = 113$). The total number of sessions across all participants was 2298. Twenty-one (16%) participants received fewer than six SRT sessions; two participants (2%) received no sessions. On average, the no-dose group received 3.88 sessions (range 0–21 sessions, SD 4.1 sessions), the partial dose group received 16.8 sessions (range 6–32 sessions, SD 6.6 sessions) and the full-dose group received 20.2 sessions (range 7–33 sessions, SD 5.0 sessions).

Competence

Seventy-five sessions (3.3%) were rated for competence by 1–10 raters. The mean CTS-R score was 47.2 (range 33–63, SD 6.5) and 97% ($n = 73$) of all sessions were rated as competent, which reflects a CTS-R score of ≥ 36. Agreement among raters regarding competence status was 95%.

Main trial results

Summary of main trial results

There was no evidence of the superiority of SRT plus ESC to ESC alone. There were no consistent significant differences between the two trial arms. On the primary outcome, time spent in structured activity at 15 months, the level of missing data was 13%, with 11 (4%) participants missing in the SRT plus ESC arm and 24 (9%) participants missing in the ESC-alone arm. For the other assessments, missing data rates were higher. At 15 months, for the interview-based psychopathology assessments (SCID and CAARMS) 27% of data were missing: 30 participants (11%) in the SRT plus ESC arm and 44 participants (16%) in the ESC alone arm. For self-report measures (BDI depression, SIAS social anxiety, BHS hopelessness and SSI schizotypal experiences), 23% of data were missing at 15 months: 23 participants (9%) in the SRT plus ESC arm and 38 participants (14%) in the ESC-alone arm. There was a consistent trend for higher levels of missingness of data in the ESC-alone arm than in the SRT arm, particularly at 15 months. Rates of missingness of data were substantially less at 9 months, with less discrepancy in missingness of data between arms. The level of missingness of data and data patterns were reviewed by the statistical team and agreed to be suitable for the ITT analysis using a general linear model.

Intention-to-treat analysis of primary outcome

The primary outcome was prespecified to be levels of structured activity at 15 months. There was no evidence of any superiority of SRT over ESC or consistent differences in levels of structured activity at 15 months (both including and excluding levels of child care) (*Table 15*).

Including an interaction term for either of the mental state (ARMS vs. not at risk) or functioning (low vs. very low levels of structured activity) stratifiers did not have an impact on findings (see *Appendix 3*, *Table 40*). Therefore, there was no evidence for the superiority of SRT irrespective of participant ARMS or functioning status at baseline.

TABLE 15 Primary time use outcomes: analysis of ITT population at 15 and 9 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
15 months						
Structured activity (hours per week)	22.4 (21.4)	27.7 (26.5)	−4.44 (−10.19 to 1.31)	0.13	−0.12 (−0.34 to 0.10)	0.29
Missing, *n*	11	24				
Structured activity (minus child care) (hours per week)	21.1 (18.1)	24.9 (20.4)	−2.98 (−7.49 to 1.53)	0.19	−0.08 (−0.29 to 0.13)	0.46
Missing, *n*	11	24				
9 months						
Structured activity (hours per week)	21.4 (16.6)	22.3 (19.3)	−0.90 (−5.02 to 3.21)	0.67	0.07 (−0.14 to 0.28)	0.50
Missing, *n*	12	17				
Structured activity (minus child care) (hours per week)	20.3 (14.7)	22.2 (19.3)	−1.71 (−5.67 to 2.26)	0.40	0.06 (−0.15 to 0.27)	0.57
Missing, *n*	12	17				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

Analysis of secondary and other outcomes

There was no evidence of any superiority of SRT over ESC, or evidence for consistent differences in structured activity at 9 months or in constructive economic activity at 15 months (*Table 16*). There was no evidence of superiority of SRT in total levels of employment, education and voluntary work activity. As there were no consistent statistically significant differences between the intervention and the control groups in the primary or secondary outcomes, mediation and moderation analyses were not conducted.

Secondary psychopathology outcomes were analysed using general linear models, adjusting for baseline values (of the outcome variable), stratification variables and neurocognitive performance. Data for CAARMS symptom severity at 9 months, and the suicidality severity score at 9, 15 and 24 months, were found to be highly skewed and, therefore, a log-transformation on the outcome variable was used. There was no evidence of any superiority of SRT over ESC or consistent differences in levels of psychopathology, as assessed by ARMS symptom severity or distress rate (*Table 17*), in diagnosable depression or anxiety disorder (*Tables 18* and *19*), or in self-reported psychopathology (*Tables 20* and *21*) or other outcomes (*Table 22*). For all secondary psychopathology outcomes there were more missing data in the ESC-alone arm than in the SRT plus ESC arm. At 15 months, the rate of missing data in the ESC-alone arm was typically double that in the intervention arm.

TABLE 16 Secondary time use outcomes: analysis of ITT population at 15 and 9 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
15 months						
Constructive economic activity (hours per week)	17.4 (19.9)	22.0 (24.5)	−4.44 (−9.88 to 1.01)	0.11	−0.22 (−0.46 to 0.03)	0.085
Missing, *n*	11	24				
Total hours paid employment[d]	75.3 (213.8)	123.6 (275.2)	−47.03 (−111.53 to 17.47)	0.15	−0.30 (−0.92 to 0.31)	0.34
Missing, *n*	21	31				
Total hours education[d]	76.6 (174.1)	88.8 (176.3)	−12.35 (−59.48 to 34.79)	0.61	−0.26 (−0.90 to 0.38)	0.43
Missing, *n*	25	31				
Total hours voluntary employment[d]	16.5 (46.8)	36.8 (96.3)	−19.21 (−39.35 to 0.93)	0.062	−0.25 (−0.75 to 0.24)	0.32
Missing, *n*	27	28				
Total hours all activity[d]	158.8 (252.0)	258.8 (359.8)	−93.04 (−175.93 to −10.15)	0.028	−0.46 (−1.13 to 0.21)	0.18
Missing, *n*	34	35				
9 months						
Constructive economic activity (hours per week)	15.7 (14.3)	16.6 (15.9)	−1.14 (−4.74 to 2.45)	0.53	−0.01 (−0.24 to 0.23)	0.95
Missing, *n*	12	17				
Total hours paid employment[d]	156.9 (432.3)	283.9 (511.4)	−106.66 (−239.19 to 25.87)	0.11	−0.65 (−1.45 to 0.14)	0.11
Missing, *n*	25	48				
Total hours education[d]	130.1 (353.3)	108.0 (235.0)	23.74 (−66.66 to 114.15)	0.61	0.18 (−0.55 to 0.91)	0.63
Missing, *n*	26	50				
Total hours voluntary employment[d]	50.5 (215.4)	50.7 (170.9)	−4.04 (−60.84 to 52.77)	0.89	−0.11 (−0.71 to 0.48)	0.71
Missing, *n*	33	47				
Total hours all activity[d]	349.1 (591.2)	454.2 (592.9)	−88.83 (−259.47 to 81.81)	0.31	−0.43 (−1.22 to 0.37)	0.29
Missing, *n*	35	56				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

TABLE 17 Secondary outcomes: CAARMS severity and distress secondary outcomes at 9 and 15 months

Severity and distress outcomes	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
9 months						
CAARMS symptom severity score	28.4 (21.5)	27.1 (18.7)	2.26 (−1.92 to 6.43)	0.29	0.09 (−0.13 to 0.32)	0.40
Missing, *n*	21	28				
CAARMS average distress score	47.5 (27.5)	44.7 (24.3)	2.11 (−3.73 to 7.95)	0.48		
Missing, *n*	27	28				
CAARMS aggression severity score	6.2 (5.4)	6.2 (5.8)	0.57 (−0.75 to 1.89)	0.40		
Missing, *n*	15	18				
CAARMS suicidality severity score	5.7 (6.9)	4.5 (5.8)	0.98 (−0.55 to 2.51)	0.21	0.14 (−0.13 to 0.42)	0.31
Missing, *n*	15	17				
15 months						
CAARMS symptom severity score	23.4 (21.0)	24.3 (18.9)	0.29 (−4.35 to 4.94)	0.90		
Missing, *n*	23	42				
CAARMS average distress score	43.4 (28.1)	39.7 (25.8)	4.09 (−3.52 to 11.70)	0.29		
Missing, *n*	34	40				
CAARMS aggression severity score	5.6 (5.7)	5.5 (6.1)	0.62 (−0.89 to 2.12)	0.42		
Missing, *n*	11	32				
CAARMS suicidality severity score	4.4 (6.1)	3.8 (6.1)	0.82 (−0.74 to 2.39)	0.30	0.21 (−0.09 to 0.50)	0.17
Missing, *n*	15	33				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
CAARMS symptom severity reflects the product of global severity (scored 0–6) and frequency (scored 0–6) for four positive symptom subscales. CAARMS distress reflects the average distress score (scored 0–100) for four positive symptom subscales. CAARMS aggression and suicidality severity scores reflect the respective products of global severity (scored 0–6) and frequency scores (scored 0–6). Higher scores reflect more severe symptoms.

Past mood and infrequently endorsed anxiety, eating and somatoform diagnoses are presented in *Appendix 3*, *Analysis of general psychopathology diagnoses continued*. The majority of participants met diagnostic criteria for a current major depressive episode (see *Table 18*) and almost half met criteria for current social phobia (see *Table 19*).

As secondary outcome measures, self-report questionnaire data were analysed using general linear models, adjusting for the stratification variables, neurocognitive performance and differences in the outcome variable at baseline (see *Tables 20* and *21*).

TABLE 18 Secondary outcomes: SCID diagnoses (1) mood outcomes at 9 and 15 months

Mood outcome	Time point	Prevalence, *n* (%), *n* missing		Relative risk[a] (95% CI[b])	*p*-value[c]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Current major depressive episode	Baseline	72 (52), 0	65 (49), 0		
	9 months	26 (21), 13	33 (29), 19	0.71 (0.46 to 1.11)	0.18
	15 months	35 (29), 16	26 (26), 31	1.11 (0.72 to 1.72)	0.65
Current mania	Baseline	1 (0.7), 0	1 (0.8), 0		
	9 months	1 (0.8), 13	2 (1.8), 20	0.45 (0.04 to 4.87)	0.60
	15 months	0 (0), 16	2 (2.0), 30	–	0.21
Current hypomania	Baseline	5 (3.6), 0	2 (1.5), 0		
	9 months	2 (1.6), 13	2 (1.8), 20	0.90 (0.13 to 6.26)	1.00
	15 months	1 (0.8), 16	2 (2.0), 30	0.42 (0.04 to 4.54)	0.59
Dysthymia	Baseline	16 (12), 0	15 (11), 0		
	9 months	13 (10), 13	8 (7.1), 20	1.46 (0.63 to 3.38)	0.49
	15 months	15 (12), 16	7 (6.9), 31	1.77 (0.75 to 4.18)	0.26
Bipolar at risk	Baseline	25 (18), 0	14 (11), 0		
	9 months	6 (4.8), 13	11 (9.8), 20	0.49 (0.19 to 1.28)	0.21
	15 months	8 (6.6), 16	6 (5.9), 31	1.10 (0.40 to 3.08)	1.00
Bipolar I	Baseline	2 (1.5), 0	5 (3.8), 0		
	9 months	3 (2.4), 13	5 (4.5), 20	0.54 (0.13 to 2.20)	0.48
	15 months	2 (1.6), 16	5 (4.9), 30	0.33 (0.07 to 1.69)	0.25
Bipolar II	Baseline	4 (2.9), 0	1 (0.8), 0		
	9 months	3 (2.4), 13	2 (1.8), 20	1.34 (0.23 to 7.90)	1.00
	15 months	2 (1.6), 16	0 (0), 30	–	0.50

a A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
b Asymptotic Wald 95% confidence limits.
c The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

Outcomes for negative symptoms (SANS) are presented in *Appendix 3*, *Analysis of negative symptoms*. There was no consistent evidence of the superiority of SRT plus ESC over ESC alone with respect to SANS. There was no evidence for any superiority of SRT or consistent differences in levels of drug and alcohol disorders (see *Table 22*).

Analysis of maintenance of gains at 24 months

The 24-month assessment was designed as a specific add-on study. This was requested by the funders after completion of the internal pilot phase and recruitment of the first 100 participants. The original study was designed with a 9-month and 15-month assessment, with 15 months being the primary end point. The 24-month follow-up required recontacting the original 100 participants to reconsent and capture follow-up data, as they had not originally given consent for this longer-term assessment point. The subsequent 170 participants were then consented prospectively.

TABLE 19 Secondary outcomes: SCID diagnoses (2) anxiety, eating and somatoform outcomes at 9 and 15 months

Anxiety, eating and somatoform outcome	Time point	Prevalence, *n* (%), *n* missing[a]		Relative risk[b] (95% CI[c])	*p*-value[d]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Panic disorder with agoraphobia	Baseline	18 (13), 0	25 (19), 0		
	9 months	7 (41), 1	12 (55), 3	0.75 (0.38 to 1.50)	0.52
	15 months	7 (41), 1	12 (57), 4	0.72 (0.37 to 1.42)	0.52
Agoraphobia without panic	Baseline	21 (15), 0	31 (24), 0		
	9 months	10 (53), 2	18 (72), 6	0.73 (0.45 to 1.20)	0.22
	15 months	11 (58), 2	14 (58), 7	0.99 (0.60 to 1.65)	1.00
Social phobia	Baseline	62 (45), 0	54 (41), 0		
	9 months	22 (40), 7	24 (53), 9	0.75 (0.49 to 1.15)	0.23
	15 months	28 (52), 8	16 (39), 13	1.33 (0.84 to 2.11)	0.30
Specific phobia	Baseline	10 (7.3), 0	4 (3.0), 0		
	9 months	3 (30), 0	1 (25), 0	1.20 (0.17 to 8.38)	1.00
	15 months	5 (50), 0	1 (25), 0	2.00 (0.33 to 12.18)	0.58
OCD	Baseline	12 (8.7), 0	11 (8.3), 0		
	9 months	4 (33), 0	1 (10), 1	3.33 (0.44 to 25.23)	0.32
	15 months	5 (42), 0	0 (0), 3	–	0.055
PTSD	Baseline	14 (10), 0	16 (12), 0		
	9 months	5 (46), 3	5 (42), 4	1.09 (0.43 to 2.77)	1.00
	15 months	6 (55), 3	5 (46), 5	1.20 (0.52 to 2.79)	1.00
GAD	Baseline	36 (26), 0	44 (33), 0		
	9 months	11 (33), 3	16 (44), 8	0.75 (0.41 to 1.37)	0.46
	15 months	13 (41), 4	10 (30), 11	1.34 (0.69 to 2.61)	0.44
Body dysmorphic disorder	Baseline	14 (10), 0	10 (7.6), 0		
	9 months	8 (62), 1	2 (29), 3	2.15 (0.62 to 7.50)	0.35
	15 months	8 (67), 2	2 (29), 3	2.33 (0.68 to 8.04)	0.17

GAD, generalised anxiety disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder.

a For category (2) variables, baseline prevalence is based on the total number (*N*) within the relevant group. For 9, 15 and 24 months, for each diagnosis, the prevalence is based on the total number at baseline with a positive diagnosis (discounting 'missing' or negative diagnosis at baseline).

b A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.

c Asymptotic Wald 95% confidence limits.

d The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

On the primary outcome of time spent in structured activity, the proportion of missing data at 24 months was 24% (65 participants). There were 25 participants in the treatment group (9%) and 40 participants in the control group (15%) with missing data. CAARMS symptom severity data were unavailable for > 50% of participants, so these data were unusable. CAARMS transition to psychosis data were missing for 34% of participants: 15% in the treatment group and 19% in the control group. SCID psychopathology data were missing for 30% of participants: 12% in the treatment group and 18% in the control group. Self-report psychopathology data were missing for 33% of participants: 14% in the treatment group and 19% in the control group.

TABLE 20 Secondary outcomes: emotional disturbance at 9 and 15 months

Emotional disturbance	Allocation arm, mean (SD)		Adjusted difference[a] (95% CI[b])	*p*-value[c]
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
9 months				
SIAS score	44.1 (16.9)	44.0 (15.6)	−2.56 (−6.13 to 1.01)	0.16
Missing, *n*	23	29		
BDI-II score	18.6 (15.4)	19.9 (13.7)	−1.28 (−4.83 to 2.26)	0.48
Missing, *n*	24	32		
15 months				
SIAS score	43.1 (17.7)	42.2 (17.7)	−0.45 (−4.84 to 3.95)	0.84
Missing, *n*	23	38		
BDI-II score	19.2 (15.7)	19.4 (14.9)	−0.32 (−4.06 to 3.42)	0.87
Missing, *n*	25	38		

BDI-II, Beck Depression Inventory-II.
a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
SIAS is a total score on 20 items, each scored from 0 to 4, with higher scores reflecting greater symptomatic severity. A total score ≥ 43 reflects social phobia or social anxiety disorder. Beck Depression Inventory-II is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater symptomatic severity. A total score ≥ 29 reflects severe depression.

TABLE 21 Secondary outcomes: emotional disturbance at 9 and 15 months further data

Emotional disturbance	Allocation arm, mean (SD)		Adjusted difference[a] (95% CI[b])	*p*-value[c]
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
9 months				
GAF	49.7 (15.8)	48.6 (14.9)	1.57 (−2.12 to 5.27)	0.40
Missing, *n*	17	26		
GAS	52.2 (15.2)	51.2 (14.1)	1.02 (−2.51 to 4.56)	0.57
Missing, *n*	17	26		
SOFAS	51.7 (15.5)	53.4 (16.5)	0.24 (−3.37 to 3.84)	0.90
Missing, *n*	17	26		
15 months				
GAF	50.8 (18.0)	51.9 (17.4)	−0.93 (−5.24 to 3.38)	0.67
Missing, *n*	21	37		
GAS	54.2 (16.0)	55.6 (17.9)	−1.72 (−5.95 to 2.51)	0.43
Missing, *n*	21	35		
SOFAS	54.6 (17.3)	55.8 (19.4)	0.60 (−3.64 to 4.84)	0.78
Missing, *n*	20	35		

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
GAF is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in symptomatic and functional problems. GAS is an observer-rated score from 0 to 100, with lower scores reflecting greater symptom severity. SOFAS is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in functional problems.

TABLE 22 Other outcomes at 9 and 15 months

Outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
9 months						
BHS score	9.2 (6.2)	9.1 (5.9)	−0.17 (−1.70 to 1.36)	0.83		
Missing, *n*	28	33				
AUDIT	4.6 (6.6)	4.4 (5.1)	0.52 (−0.67 to 1.71)	0.39	0.01 (−0.20 to 0.22)	0.92
Missing, *n*	23	29				
DUDIT	3.1 (6.6)	3.8 (7.8)	−0.71 (−2.02 to 0.61)	0.29	−0.08 (−0.28 to 0.12)	0.42
Missing, *n*	19	28				
15 months						
BHS score	9.5 (6.1)	9.5 (6.4)	−0.17 (−1.80 to 1.47)	0.84		
Missing, *n*	22	39				
AUDIT	4.6 (6.0)	4.5 (6.0)	0.63 (−0.69 to 1.95)	0.35	0.08 (−0.14 to 0.30)	0.46
Missing, *n*	22	35				
DUDIT	2.6 (5.7)	3.4 (7.9)	−1.05 (−2.54 to 0.45)	0.17	−0.08 (−0.30 to 0.14)	0.46
Missing, *n*	19	39				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
BHS is a total score on 20 items, each scored 0 or 1, with higher scores reflecting greater hopelessness. A total score of 9–14 reflects moderate hopelessness. AUDIT is a total score on 10 items, each scored from 0 to 4, with higher scores reflecting greater alcohol use. A total score of 1–7 indicates low risk, with a score ≥ 8 reflecting hazardous drinking and ≥ 15 reflecting potential alcohol dependence. DUDIT is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater drug use. There are no published clinically relevant DUDIT thresholds.

Outcomes at 24 months suggest that the clinically important gains in both arms on structured activity (*Table 23*), general psychopathology (*Tables 24–26*) and other outcomes (*Table 27*) at 9 and 15 months are maintained at 24 months.

The ITT analysis provides no evidence for superiority of SRT over ESC on any primary or secondary outcome at 24 months. There was weak evidence for superiority of SRT plus ESC over ESC alone for the other outcome of reduction of substance misuse as measured by the DUDIT at 24 months (see *Table 27*). On one dimension of secondary outcome (constructive economic activity) there was evidence of a consistent difference in favour of the ESC-alone arm (see *Table 23*). The PP analysis (*Table 28*) was conducted for time use variables at 24 months and supported the ITT model.

TABLE 23 Time use outcomes: analysis of ITT population at 24 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	24.3 (18.9)	32.4 (28.7)	−7.51 (−13.91 to −1.12)	0.022	−0.20 (−0.45 to 0.04)	0.099
Missing, *n*	25	40				
Structured activity (minus child care) (hours per week)	23.8 (18.9)	26.6 (20.4)	−2.37 (−7.59 to 2.84)	0.370	−0.09 (−0.33 to 0.16)	0.48
Missing, *n*	25	40				
Constructive economic activity (hours per week)	18.6 (16.7)	27.4 (28.0)	−8.34 (−14.41 to −2.27)	0.007	−0.28 (−0.55 to −0.02)	0.038
Missing, *n*	25	40				
Total hours education[d]	76.7 (175.3)	93.6 (182.4)	−16.88 (−66.60 to 32.85)	0.504	−0.27 (−0.93 to 0.39)	0.42
Missing, *n*	32	39				
Total hours voluntary employment[d]	14.3 (37.7)	38.3 (99.7)	−24.10 (−44.78 to −3.42)	0.023	−0.31 (−0.82 to 0.20)	0.23
Missing, *n*	34	36				
Total hours all activity[d]	161.0 (255.0)	258.9 (364.5)	−92.86 (−179.00 to −6.72)	0.035	−0.46 (−1.15 to 0.24)	0.20
Missing, *n*	39	40				
Total hours paid employment[d]	79.1 (218.8)	121.7 (277.7)	−41.41 (−108.58 to 25.76)	0.226	−0.25 (−0.88 to 0.39)	0.439
Missing, *n*	27	37				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity hours of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 24 Secondary outcomes: SCID diagnoses (1) mood outcomes at 24 months

Mood outcome	Time point	Prevalence, *n* (%), *n* missing		Relative risk[a] (95% CI[b])	*p*-value[c]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Current major depressive episode	Baseline	72 (52.2), 0	65 (49.2), 0		
	24 months	24 (22.6), 32	18 (21.7), 49	1.04 (0.61 to 1.79)	1.00
Past major depressive episode	Baseline	33 (23.9), 0	41 (31.1), 0		
	24 months	24 (22.6), 32	12 (14.6), 50	1.55 (0.82 to 2.91)	0.19
Current mania	Baseline	1 (0.7), 0	1 (0.8), 0		
	24 months	2 (1.9), 32	0 (0), 49	–	0.51
Past mania	Baseline	2 (1.5), 0	5 (3.8), 0		
	24 months	2 (1.9), 32	1 (1.2), 49	1.57 (0.14 to 16.98)	1.00
Current hypomania	Baseline	5 (3.6), 0	2 (1.5), 0		
	24 months	2 (1.9), 32	2 (2.4), 49	0.78 (0.11 to 5.44)	1.00

continued

TABLE 24 Secondary outcomes: SCID diagnoses (1) mood outcomes at 24 months (*continued*)

Mood outcome	Time point	Prevalence, *n* (%), *n* missing: SRT + ESC (*N* = 138)	Prevalence, *n* (%), *n* missing: ESC alone (*N* = 132)	Relative risk[a] (95% CI[b])	*p*-value[c]
Past hypomania	Baseline	2 (1.5), 0	1 (0.8), 0		
	24 months	2 (1.9), 32	2 (2.4), 49	0.78 (0.11, to 5.44)	1.00
Dysthymia	Baseline	16 (11.6), 0	15 (11.4), 0		
	24 months	20 (18.9), 32	7 (8.4), 49	2.24 (0.99 to 5.04)	0.058
Bipolar at risk	Baseline	25 (18.1), 0	14 (10.6), 0		
	24 months	11 (10.4), 32	6 (7.3), 50	1.42 (0.55 to 3.67)	0.61
Bipolar I	Baseline	2 (1.5), 0	5 (3.8), 0		
	24 months	4 (3.8), 32	1 (1.2), 50	3.09 (0.35 to 27.16)	0.39
Bipolar II	Baseline	4 (2.9), 0	1 (0.8), 0		
	24 months	2 (1.9), 32	1 (1.2), 50	1.55 (0.14 to 16.77)	1.00
Major depressive disorder	Baseline	95 (68.8), 0	93 (70.5), 0		
	24 months	45 (42.5), 32	28 (33.7), 49	1.26 (0.87 to 1.83)	0.23

a A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
b Asymptotic Wald 95% confidence limits.
c The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

TABLE 25 Secondary outcomes: SCID diagnoses (2) anxiety, eating and somatoform outcomes at 24 months

Anxiety, eating and somatoform outcome	Time point	Prevalence, *n* (%), *n* missing[a]: SRT + ESC (*N* = 138)	Prevalence, *n* (%), *n* missing[a]: ESC alone (*N* = 132)	Relative risk[b] (95% CI[c])	*p*-value[d]
Panic disorder with agoraphobia	Baseline	18 (13), 0	25 (19), 0		
	24 months	4 (29), 4	4 (22), 7	1.29 (0.39 to 4.26)	0.71
Agoraphobia without panic	Baseline	21 (15), 0	31 (24), 0		
	24 months	7 (44), 5	9 (45), 11	0.97 (0.47 to 2.03)	1.00
Social phobia	Baseline	62 (45), 0	54 (41), 0		
	24 months	27 (59), 16	13 (36), 18	1.63 (0.99 to 2.67)	0.049
Specific phobia	Baseline	10 (7.3), 0	4 (3.0), 0		
	24 months	4 (57), 3	1 (33), 1	1.71 (0.31 to 9.61)	1.00
OCD	Baseline	12 (8.7), 0	11 (8.3), 0		
	24 months	3 (27.3), 1	0 (0), 3	–	0.23
PTSD	Baseline	14 (10), 0	16 (12), 0		
	24 months	2 (20), 4	4 (50), 8	0.40 (0.10 to 1.66)	0.32
GAD	Baseline	36 (26), 0	44 (33), 0		
	24 months	13 (48), 9	11 (42), 18	1.14 (0.63 to 2.06)	0.79
Body dysmorphic disorder	Baseline	14 (10), 0	10 (7.6), 0		
	24 months	4 (36.4), 3	0 (0), 4		

GAD, generalised anxiety disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.
a For category (2) variables, baseline prevalence is based on the total number (*N*) within the relevant group. For 9 months, 15 months and 24 months, for each diagnosis, the prevalence is based on the total number at baseline with a positive diagnosis (discounting 'missing', or negative diagnosis at baseline).
b A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
c Asymptotic Wald 95% confidence limits.
d The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

TABLE 26 Secondary outcomes: emotional disturbance at 24 months

Emotional disturbance	Allocation arm, mean (SD)		Adjusted difference[a] (95% CI[b])	*p*-value[c]
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
SIAS score	43.9 (17.6)	41.3 (17.4)	1.48 (−3.50 to 6.45)	0.56
Missing, *n*	39	49		
BDI-II score	18.0 (15.7)	17.5 (14.8)	1.93 (−2.22 to 6.08)	0.36
Missing, *n*	41	51		
GAF	50.3 (17.2)	53.4 (16.2)	−2.87 (−7.49 to 1.76)	0.22
Missing, *n*	36	51		
GAS	53.3 (17.6)	56.6 (16.6)	−3.63 (−8.40 to 1.14)	0.14
Missing, *n*	38	50		
SOFAS	53.3 (18.1)	57.4 (19.4)	−2.05 (−6.91 to 2.81)	0.41
Missing, *n*	38	50		

BDI-II, Beck Depression Inventory-II.
a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
SIAS is a total score on 20 items, each scored from 0 to 4, with higher scores reflecting greater symptomatic severity. A total score ≥ 43 reflects social phobia or social anxiety disorder. The Beck Depression Inventory-II is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater symptomatic severity. A total score ≥ 29 reflects severe depression. GAF is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in symptomatic and functional problems. GAS is an observer-rated score from 0 to 100, with lower scores reflecting greater symptom severity. SOFAS is an observer-rated score from 0 to 100, with lower scores reflecting greater severity in functional problems.

TABLE 27 Other outcomes at 24 months

Outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
BHS score	9.6 (6.1)	7.8 (6.2)	1.40 (−0.34 to 3.14)	0.12		
Missing, *n*	40	52				
AUDIT	3.5 (4.3)	3.7 (3.3)	0.24 (−0.68 to 1.16)	0.60	−0.12 (−0.35 to 0.10)	0.27
Missing, *n*	36	49				
DUDIT	2.1 (6.0)	3.3 (7.3)	−1.36 (−2.86 to 0.14)	0.075	−0.29 (−0.51 to −0.06)	0.013
Missing, *n*	34	47				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
BHS is a total score on 20 items, each scored 0 or 1, with higher scores reflecting greater hopelessness. A total score of 9–14 reflects moderate hopelessness. AUDIT is a total score on 10 items, each scored from 0 to 4, with higher scores reflecting greater alcohol use. A total score of 1–7 indicates low risk, with a score ≥ 8 reflecting hazardous drinking and ≥ 15 potential alcohol dependence. DUDIT is a total score on 21 items, each scored from 0 to 3, with higher scores reflecting greater drug use. There are no published clinically relevant DUDIT thresholds.

TABLE 28 Time use outcomes: analysis of PP population at 24 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	22.4 (18.0)	32.4 (28.7)	−8.75 (−16.07 to −1.42)	0.020	−0.27 (−0.54 to 0.01)	0.059
Missing, *n*	12	40				
Structured activity (minus child care) (hours per week)	21.9 (18.0)	26.6 (20.4)	−3.94 (−9.69 to 1.82)	0.18	−0.16 (−0.43 to 0.12)	0.26
Missing, *n*	12	40				
Constructive economic activity (hours per week)	17.9 (16.4)	27.4 (28.0)	−7.97 (−15.02 to −0.93)	0.027	−0.28 (−0.59 to 0.03)	0.073
Missing, *n*	12	40				
Total hours paid employment[d]	42.9 (112.1)	121.7 (277.7)	−73.53 (−141.04 to −6.02)	0.033	−0.55 (−1.24 to 0.15)	0.12
Missing, *n*	14	37				
Total hours education[d]	58.8 (141.4)	93.6 (182.4)	−32.55 (−84.01 to 18.92)	0.21	−0.23 (−0.96 to 0.49)	0.52
Missing, *n*	16	39				
Total hours voluntary employment[d]	17.2 (41.7)	38.3 (99.7)	−18.98 (−43.61 to 5.66)	0.13	−0.08 (−0.66 to 0.51)	0.80
Missing, *n*	17	36				
Total hours all activity[d]	118.7 (172.4)	258.9 (364.5)	−132.41 (−224.74 to −40.09)	0.005	−0.48 (−1.25 to 0.29)	0.22
Missing *n*	21	40				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity hours per week of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

The missing data analysis (see *Appendix 3, Analysis of missing data for primary outcome* and *Analysis of missing data: comparison of methods*) is consistent with the ITT analysis, suggesting that there is no evidence for the superiority of SRT over ESC alone at the 24-month assessment. The missing data analyses and PP analysis are consistent with the ITT analysis in providing weak evidence of a consistent difference in favour of the ESC-alone arm. However, these results need to be interpreted with some caution. Both methods used to mitigate against bias from missing data (i.e. FIML and MI) do so only on the assumption that data are missing at random. If this assumption does not hold (i.e. when data are missing not at random), biased estimates may still occur as a result of the missing data.

Serious adverse events

All serious adverse events (SAEs) and adverse events (AEs) were categorised and recorded from randomisation until completion of the final follow-up assessment. Definitions used for delineating events are provided in *Appendix 4*. All events were reported to the chief investigator, sponsor, local trial site, Clinical Trials Unit, and trial oversight committees (i.e. DMEC and TSC). All SAEs were reviewed by a clinician independent of the trial for possible relatedness. SAEs would have been reported to the NHS REC, as appropriate (i.e. deemed possibly related to the trial). Zero events were considered possibly related to the trial and, thus, none was reported to the REC. The frequency and nature of SAEs and AEs are reported in *Tables 29–31*.

Frequencies of AEs and SAEs are shown in *Table 29*. There were 167 reportable AEs in the trial, 83 of which were considered serious. All events were considered unrelated to the trial. It is noted that events are clustered around individuals (i.e. individuals who frequently report more than one event); therefore, the number of events exceeds the number of individuals reporting them. Moreover, an excess of both SEs and AEs in the intervention arm is noted. This excess can be explained according to the reporting mechanism (see *Table 30*). The number of AEs reported to RAs at assessment points was the same or very similar in both groups, but a subset of individuals in the intervention arm reported AEs to therapists during the intervention period, a mechanism that was not available to participants in the ESC-alone arm.

TABLE 29 Adverse event summary

	Allocation arm, *n* (%)			
	SRT + ESC		ESC alone	
Event type	Events	Individuals	Events	Individuals
Any event	105	48 (35)	62	32 (24)
AEs	52	35 (25)	32	24 (18)
SAEs	53	26 (19)	30	16 (12)
Adverse reactions	0	0 (0)	0	0 (0)
Unexpected adverse reactions	0	0 (0)	0	0 (0)
Serious adverse reactions	0	0 (0)	0	0 (0)
Suspected unexpected serious adverse reactions	0	0 (0)	0	0 (0)

TABLE 30 Adverse events by reporting mechanism

	Allocation arm, *n* (%)			
	SRT + ESC		ESC alone	
Reporting mechanism	Events	Individuals	Events	Individuals
AE reported to research therapist	17	14	0	0
SAE reported to research therapist	17	12	0	0
AE reported to RA	35	25	32	24
SAE reported to RA	36	22	30	16
9-month assessment	6	6 (4.8)	10	10 (8.7)
15-month assessment	17	13 (10)	9	7 (6.5)
24-month assessment	13	11 (9.6)	11	7 (7.6)

TABLE 31 Nature of adverse events

Event type	Allocation arm (*n*)			
	SRT + ESC (*N* = 138)		ESC alone (*N* = 132)	
	Events	Individuals	Events	Individuals
SAE				
Potentially/life-threatening self-harm	1	1	2	2
Medication or substance overdose	16	10	10	7
Medication/substance overdose resulting in hospital admission	5	4	1	1
Potentially/life-threatening road behaviour	2	1	0	0
Potentially/life-threatening overdose and self-harm	1	1	0	0
Suicidal intent	7	6	1	1
Suicide attempt				
Medication overdose	7	7	3	3
Medication overdose resulting in hospital admission	1	1	2	1
Self-harm, self-poisoning and/or ligature use	4	4	3	3
Overdose and self-harm resulting in hospital admission	1	1	1	1
Other	3	3	4	3
Assault on participant	1	1	0	0
Hospitalisation				
Psychiatric	3	3	0	0
General	1	1	2	2
Other	0	0	1	1
AE				
Suicidal ideation	13	10	6	6
Self-harm	12	11	9	7
Medication overdose	2	2	2	2
Assault by participant	1	1	0	0
Physical/sexual assault on participant	2	2	0	0
General medical assessment/procedure	2	2	3	3
Bereavement	1	1	1	1
Escalation in alcohol and/or substance use	4	3	3	2
Thoughts of harming others	3	3	0	0
Police cell admission	1	1	0	0
Acute anxiety and/or tearfulness	0	0	3	3
Deterioration in mental health	1	1	2	2

A discrepancy remained (see *Table 30*) in that more individuals in the SRT plus ESC arm than in the ESC-alone arm reported SAEs to researchers. However, it is also notable that the proportion of participants who completed all follow-ups was greater in the SRT plus ESC arm; therefore, events reported to researchers were further delineated with respect to follow-up point to allow SAEs to be calculated as proportions of completers. A smaller proportion of participants in the SRT plus ESC arm reported a lower number of SAEs to researchers at their 9-month assessment than participants in the ESC arm. At 15 and 24 months, a slightly higher percentage of SRT plus ESC participants reported SAEs to the researcher than participants in the ESC arm. In summary, apparent differences in the number of AEs appear to be due to the reporting mechanism and differences in the rates of missing data between the groups.

As shown in *Table 31*, the nature of AEs was similar in arms and was as expected in this vulnerable population group. The most commonly reported AEs and SAEs centred around suicidal ideation, self-harm and overdose behaviours, and suicide attempts.

Chapter 5 Health economic findings

Abstract

Objective
To estimate the cost-effectiveness of the SRT intervention, compared with ESC, a within-trial cost–utility analysis was undertaken.

Methods
A within-trial analysis was conducted, where costs and benefits were estimated over a 24-month period and discounted at 3.5% in the second year. Costs were estimated from the perspective of the NHS and Personal Social Services (PSS), at 2017/18 levels, and included intervention (training, therapy session and supervision) costs and other health professional and hospital admission costs. Total quality-adjusted life-year (QALY) scores were estimated from the EQ-5D-3L responses. Regression was undertaken to estimate the incremental cost-effectiveness ratio (ICER) (mean incremental cost/mean QALY gain), where value for money would correspond to an ICER below the cost-effectiveness threshold (λ) value of £20,000 per QALY. The level of uncertainty, according to the cost-effectiveness acceptability curve (CEAC), was also assessed at the same λ value. MI was used in the base-case analysis.

Results
Based on 270 patients, the mean incremental cost for SRT, compared with ESC, was estimated to be £3910.59 (95% CI £2708.32 to £5112.86), with a QALY gain of 0.001 (95% CI −0.099 to 0.10). Accordingly, the ICER was estimated to be > £5M, with a low level of uncertainty.

Conclusions
Social recovery therapy was estimated to be significantly more costly than ESC and there was no significant difference in outcome, and a low level of uncertainty. Consequently, SRT was not estimated to constitute value for money.

Background

Background
The protocol for this study, with associated rationale, inclusion criteria, setting and intervention descriptions, has been published.[1] In this chapter, we report the methods and results for the economic evaluation component of the study.

Objectives
In order to estimate the cost-effectiveness of the SRT intervention, compared with ESC, a within-trial (24-month) cost–utility analysis was undertaken.

Methods

Estimating costs
Costs were estimated from the perspective of the NHS and PSS at 2017/18 levels. Below, the methods used to measure and value the intervention costs and other NHS and PSS costs are outlined.

Intervention (social recovery therapy) cost

Training

All therapists who delivered the intervention in the study received training. For costing purposes, informed by our knowledge of who delivered the intervention in the study, the therapists were assumed, on average, to be NHS band 7, and thereby have a cost per hour of employment of £53.21[79] (*Table 32*). Those who delivered the training were assumed to have a cost per hour of employment of £63.00 (grade 8a).[79] It was assumed that each therapist received 3 days of training (excluding research-related activities), with an average of four therapists receiving the training at one time, and the associated preparation/travel costs were assumed to be negligible. Total training costs (for both the trainer and therapists) were subsequently estimated, summed and equally apportioned across all intervention participants. The assumption to apportion costs to the trial participants only was in line with previous research,[83] and was undertaken as we would rather be conservative and not underestimate such costs.

Therapy sessions

To inform the assumptions about cost of intervention delivery, discussions took place with two therapists who delivered the intervention (one face-to-face meeting, followed by a number of e-mail discussions). In addition, therapists were asked to record in the database the duration of all face-to-face contacts. Details of other non-contact patient-related activities (e.g. e-mails and telephone calls) could also be recorded. After examining these data and following discussions with the therapists, it was concluded that these data were likely to be under-reported and that some therapists were better at recording non-contact activities than others. Previously, it had also been estimated that for every hour of face-to-face contact time there was an associated hour of non-contact time.[80] Two therapists were asked whether or not they thought that this reflected their practice. They thought that the most appropriate assumption was

TABLE 32 Estimated unit costs: most commonly reported (information sources)

Resource use	Unit cost (£)
Intervention costs	
Therapists (cost per hour of employment)	£53.21[79]
Trainer (cost per hour of employment)	£63.00[79]
1 hour of face-to-face contact time with therapist	£106.42[79]
Travel cost (per session)	£32.60[79]
Peer supervision (per session)	£106.42[79]
Health professional visits (most commonly reported)	
Case manager[a] (NHS band 5/6)	£70.99[79,80]
Counsellor/therapist[a]	£106.42[79,80]
GP[a]	£31.00[79]
Mental health nurse	£79.99[79,80]
Practice nurse[a]	£12.10[66,79]
Psychologist[a]	£97.55[67,79]
Psychiatrist[a]	£200.41[79]
Social worker	£79.57[79,81]
Other NHS and PSS costs	
Hospital admission (general ward)	£337.36[82]
A&E visit	£160.32[82]

A&E, accident and emergency.
a Visit reported to be in the local community.

that for every hour of face-to-face contact time there would be an associated hour of non-contact activity undertaken by the therapist for the same participant (example activities would include session reminders/bookings, liaison with other agencies and session preparation/planning). Travel time was not included in the 1 : 1 contact to non-contact time assumption and it was assumed that travel time would approximate to 30 minutes of therapist time for each face-to-face session. The associated travel costs were therefore assumed to be £6.00, on the assumption that the average associated mileage was 15 miles (the distance covered in 30 minutes of travelling at 30 miles per hour) at a cost of 40p per mile.

Supervision

Peer supervision was assumed to take place weekly (one-to-one with another therapist for 1 hour in total, including preparation) over the period when therapists were providing therapy. After estimating the total peer supervision cost for the study, this was equally apportioned across all intervention participants. Finally, the mean costs representing the cost of training, therapy provision and supervision per therapy participant were summed to estimate the mean total intervention cost (per intervention participant).

Other NHS and Personal Social Services costs

A self-reported modified version of the Client Services Receipt Inventory (CSRI[84]) was developed, which asked participants to report any contacts with health professionals (number and place) and hospital admissions (length of stay and type of ward/unit). These methods are in keeping with a previous study[39] which used a modified self-report version of the CSRI in a similar population group. Participants were asked to complete the modified CSRI at baseline (recall: previous 6 months), 9 months (recall: previous 9 months), 15 months (recall: previous 6 months) and 24 months (recall: previous 6 months); post-baseline participants were asked not to include therapy received as part of the SRT intervention (this was to enable the researchers who helped with questionnaire completion to remain blind and because this information was routinely recorded by those who provided the intervention). Control participants did not receive any specific intervention and the modified CSRI was designed to capture the standard care that they received.

Costs were assigned to each reported item of NHS and PSS resource use, with these being estimated at 2017/18 financial year levels. Subsequently, the total intervention cost (see *Supervision*) was added to the health professional and hospital admission costs to estimate the overall NHS and PSS costs.

Measuring outcomes

To estimate levels of health-related quality of life, participants were asked to complete the EQ-5D-3L[67] at baseline, and at 9, 15 and 24 months. Use of the EQ-5D was justified on the basis that this is in keeping with NICE's *Guide to the Methods of Technology Appraisal 2013*,[85] that it has been used before in similar population groups,[39] and that such use is considered to be appropriate.[86] Responses were then converted into a utility score (a scale where 0 is equal to death and 1 is full health) using the York A1 tariff.[81] The total area under the curve method (based on the assumption of linear interpolation)[82] was then used to estimate the total QALY score for each participant over the 24-month period.

Missing data assumptions

Across all time points, five participants reported that they had contact with a particular health professional, but they did not report the number of visits. Where this was the case, the average value for those who reported the number of visits was used. Similarly, four participants reported that they had had a hospital admission, but they did not report the associated length of stay, and, again, the average value for those who reported such data was used.

In the internal pilot ($n = 100$), the wrong resource use questionnaire was sent to participants at the 9-month follow-up point. The baseline questionnaire was sent rather than the 9-month questionnaire, and participants were, therefore, asked about resource use in the previous 6 months rather than in the previous 9 months. To estimate costs for the missing 3-month window post baseline, reported

levels of resource use for these 100 participants were inflated by 50% in this period. All other missing data were left as such and the corresponding individuals were excluded from the complete-case analysis.

Analysis

Three analyses were undertaken, where the following approaches were adopted in all analyses. In each, a within-trial analysis was conducted in which costs and benefits were estimated over a 24-month period, with costs incurred in the second year discounted at 3.5%.[85] A within-trial analysis, rather than a decision model, was undertaken as we are not aware of any previous studies that have compared SRT with ESC. The ITT approach was also followed, in which participants were analysed within the group to which they were allocated, regardless of, for example, the number of therapy sessions received. To estimate the mean incremental cost and incremental effect (QALY gain) associated with the intervention, compared with that for the control group, seemingly unrelated regression[87] was undertaken to allow for any correlation between costs and effects. Baseline demographic variables [age (16–19 years, 20–25 years) and sex (male/female)] were included as covariates, along with the total baseline health professional and hospital admission cost for the overall NHS and PSS cost, and the baseline EQ-5D scores for the total QALY score. In the absence of dominance (where higher costs and lower benefits were associated with a particular intervention), the incremental cost and incremental effect would be used to estimate the ICER (mean incremental cost/mean QALY gain).[85] It was also assumed that an estimated ICER below the cost-effectiveness threshold (λ) value of £20,000 per QALY[85] would suggest that an intervention constituted value for money. In addition, to estimate the level of uncertainty associated with the decision about whether or not the intervention was cost-effective, the bootstrap technique[88] (with 5000 replications) was used to estimate the probability that each intervention was cost-effective according to the CEAC.[89] In particular, the probability of SRT being cost-effective was specifically estimated at the λ of £20,000 per QALY.

The first (base-case) analysis undertaken was based on overall NHS and PSS cost, and the total QALY score, where MI[90] was used to estimate any missing data and enable all participants to be included. The MI model included costs (health professional and hospital admission costs at baseline, and at 9, 15 and 24 months, as well as total intervention costs) and outcomes (EQ-5D scores at baseline, and at 9, 15 and 24 months) and demographic variables [age, sex and social functioning (low functioning/very low functioning)]. EQ-5D scores were included, rather than individual dimension scores, as missing EQ-5D data were generally for the whole questionnaire. Health professional and hospital admission costs were, however, separated to allow for the possibility of different levels of missing data for these two variables. Two further complete-case[91] sensitivity analyses[92] were also conducted. In the first sensitivity analysis (SA1), participants were included only if they had complete cost and effect data at each time point. This enabled a comparison with the results of the base-case analysis, to assess whether or not results differed for participants who did not have missing data values imputed. A second sensitivity analysis (SA2) was also conducted, for a similar rationale, where only total intervention costs were included, as the level of missing data for this variable was anticipated to be lower.

Results

Costs

Social recovery therapy intervention cost

Training

A total of 19 therapists delivered the SRT intervention, where five group training sessions (each 3 days long) were assumed to be held. Total training costs were estimated to be £29,833.80, equating to a cost of £216.19 per participant (see *Table 33*).

TABLE 33 Social recovery therapy intervention costs

Component part (totals)	Mean per SRT participant cost (£)
Training	£216.19
Therapy sessions (including travel)	£2571.56
Supervision	£481.19
Total	£3268.94

Therapy sessions

A total of 2470 face-to-face SRT sessions were recorded across the 138 intervention participants (mean number of sessions per participant = 17.9). The mean recorded contact time per session was 63 minutes [this value was assigned to the six sessions (< 1%) where no time was recorded]. The cost of 1 hour of face-to-face contact time was estimated to be £106.42 (this includes the cost of an associated 1 hour of non-contact time). Travel costs were estimated to be £32.60 per session. Together, this meant that the mean per participant total session cost was £2571.56.

Supervision

At any one time, it was assumed that, on average over the whole study period, two SRT therapists in each of the three sites would be providing therapy and that peer supervision would, therefore, take place weekly for 1 hour between these two individuals. This was assumed to have taken place over a 5-year period in two of the sites and over a 2-year period in the third site. Over the study period, a total of 624 peer supervision sessions were thereby assumed to have taken place. At a cost of £106.42 per session, this would equate to a total cost of £66,404.68 (£481.19 per participant).

After summing the aforementioned mean cost per intervention participant training, therapy session and supervision, it was estimated that the mean total intervention cost (per SRT intervention participant) was £3268.94 (*Table 33*).

Other NHS and Personal Social Services costs

Participant response rates for the modified CSRI at baseline, and at 9, 15 and 24 months, were 270 (100%), 231 (86%), 221 (82%) and 189 (70%). Data for the participants who completed the health professional visit/hospital admission questionnaires are presented for the two groups in *Table 34*. It can be seen that, in contrast to the aforementioned intervention costs, there was comparatively little difference in mean health professional resource use/costs between the two arms. Mean hospital admission costs were seemingly higher in the intervention arm, but this difference was sensitive to a small number of participants [e.g. if data for the two participants with the longest length of stay (59 and 98 days) were not included, then the mean costs would be higher in the control arm].

Finally, overall NHS and PSS costs are presented in *Table 34*, where it can be seen that the difference in costs between groups is comparable to the cost of the intervention itself.

Outcomes

The number of participants who completed the EQ-5D at baseline, and at 9, 15 and 24 months is shown in *Table 35*. It can be seen that, based on those who responded, the mean score improved for both groups over time and the total QALY score was similar in both groups.

Analysis

The results of the regression analyses are shown in *Table 36*. In the base case, it can be seen that the overall NHS and PSS costs were, on average, £3910.59 higher for SRT participants than for ESC participants ($p < 0.01$). The total QALY score was, however, not significantly different between groups.

TABLE 34 Levels of resource use and associated costs for most commonly reported items of resource use for the 2-year follow-up period

Resource	Allocation arm, mean number of visits/number admitted to hospital (SD) [*n* with available data]; mean cost (SD)	
	SRT + ESC (*N* = 138)	**ESC alone (*N* = 132)**
Case-manager[a] (NHS band 5/6)	4.0 (10.9) [*n* = 103]; £289.66 (£786.77)	3.0 (10.8) [*n* = 78]; £218.24 (£782.20)
Counsellor/therapist[a]	5.2 (10.6) [*n* = 103]; £541.43 (£1121.66)	5.9 (10.7) [*n* = 78]; £614.38 (£1108.56)
GP[a]	9.4 (12.7) [*n* = 103]; £293.81 (£394.22)	10.6 (11.7) [*n* = 78]; £336.76 (£364.06)
Mental health nurse	1.4 (4.7) [*n* = 103]; £117.12 (£389.88)	1.8 (5.1) [*n* = 78]; £148.49 (£437.55)
Primary care nurse[a]	1.0 (2.4) [*n* = 103]; £12.91 (£29.59)	1.6 (4.4) [*n* = 78]; £21.69 (£60.70)
Psychologist[a]	0.5 (3.2) [*n* = 103]; £52.09 (£313.82)	0.5 (2.2) [*n* = 78]; £51.33 (£217.70)
Psychiatrist[a]	0.8 (1.5) [*n* = 103]; £160.95 (£307.25)	0.5 (2.2) [*n* = 78]; £51.33 (£217.70)
Social worker	0.6 (3.6) [*n* = 103]; £286.70 (£1566.36)	2.3 (9.5) [*n* = 78]; £201.49 (£832.74)
Total costs	***Mean cost (SD) [n with available data]***	***Mean cost (SD) [n with available data]***
Total health professional visit cost	£1566.36 (£1987.75) [*n* = 103]	£1926.81 (£2138.89) [*n* = 78]
Total hospital admissions cost	£1023.24 (£5160.59) [*n* = 100]	£476.30 (£1715.98) [*n* = 76]
Total other NHS and PSS costs	£2527.27 (£6121.36) [*n* = 100]	£2420.61 (£2816.77) [*n* = 76]
Intervention costs	£3268.94 (£1291.75) [*n* = 138]	–
Overall NHS and PSS costs	£5927.73 (£6148.10) [*n* = 100]	£2420.61 (£2816.77) [*n* = 76]

a Visit reported in local community.

Notes
Costs are presented for the 2-year follow-up period (without discounting) for participants who completed the 9-month, 15-month and 24-month questionnaires. Figures include the adjustment made to the 9-month responses for those in the internal pilot.

TABLE 35 Estimated EQ-5D scores at baseline, and at 9-, 15-, and 24-month follow-up points

Score	Allocation arm, *N*/mean (SD) [*n*]	
	SRT + ESC (*N* = 138)	**ESC alone (*N* = 132)**
Baseline EQ-5D-3L	0.47 (0.310) [137]	0.49 (0.275) [132]
9-month EQ-5D-3L	0.63 (0.298) [120]	0.60 (0.308) [104]
15-month EQ-5D-3L	0.63 (0.289) [119]	0.62 (0.322) [97]
24-month EQ-5D-3L	0.67 (0.249) [103]	0.71 (0.243) [85]
QALY (discounted)	1.22 (0.469) [93]	1.17 (0.477) [74]

Statistically significant $p < 0.05$.
n, number for whom data were available; *N*, number of events.

Note
QALY is over 24 months.

TABLE 36 Estimates of incremental cost, incremental effect and level of cost-effectiveness in the base-case and sensitivity analyses

Analysis (Nsrt, Nesc)	Incremental cost (95% CI)	Incremental effect (95% CI)	ICER	CEAC[a]
		QALYs (truncated at 12 months)		
Base case: imputed (138, 132)	£3910.59 (£2708.32 to £5112.86)	0.001 (–0.099 to 0.10)	£5,583,364	0%
SA1: intervention costs only: (93, 74)	£3514.31 (£3235.40 to £3793.22)	0.064 (–0.044 to 0.17)	£59,964.25	2.58%
SA2: complete case: (88, 71)	£3876.27 (£2345.36 to £5407.19)	0.059 (–0.052 to 0.17)	£66,222.83	4.8%

Nesc, number of ESC participants included in the analysis; Nsrt, number of SRT participants included in the analysis.
a Estimated probability of being cost-effective at the threshold (λ) of £20,000 per QALY according to the CEAC; costs and benefits accrued in the second year are discounted at 3.5%.

Note
QALYs are over 24 months.

Therefore, the estimated ICER exceeded the λ value of £20,000 per QALY, at which level SRT would not be deemed cost-effective or to constitute value for money. Furthermore, according to the CEAC, it was estimated that there was a low level of uncertainty associated with that result. *Table 36* shows that similar results were obtained in both sensitivity analyses that were conducted.

Changes from protocol

The protocol[1] stated that a cost-effectiveness analysis would be carried out using activity (time use) and symptoms (CAARMS); this was not conducted for the following reasons. The results of the primary analysis show that there was no evidence of any superiority of SRT over ESC for levels of structured activity at 15 months (see *Table 15*). Similarly, there was no evidence of any superiority of SRT over ESC in levels of psychopathology as assessed by CAARMS symptom severity scores (see *Table 17*). In addition to there being no statistically significant differences between groups, the numerical differences did not favour the SRT group. SRT is also more costly than ESC (see *Table 34*). Given these results, which show that SRT is more costly and no more effective than ESC, we considered that the proposed cost-effectiveness analysis would be of limited value.

Chapter 6 Discussion and conclusions

Discussion

The aim of this study was to undertake a definitive randomised trial to determine the clinical effectiveness and cost-effectiveness of SRT compared with ESC in young people who present with social withdrawal, and non-psychotic severe and complex mental health problems, and who are at risk of long-term social disability and mental illness. The primary hypothesis was that, in young people who are socially disabled and have non-psychotic severe and complex mental health problems, SRT will be superior to ESC in improving social recovery (as measured by hours in structured activity assessed on the TUS) over a 15-month follow-up period. There was no evidence of superiority of SRT over ESC at 15 months, nor at 9 or 24 months, with respect to time spent in structured activity. There was no evidence for the superiority of SRT over ESC in terms of cost-effectiveness or effects on secondary outcomes of mental health symptoms (APS and emotional disturbance). One secondary outcome, drug use, showed significant superiority in the SRT plus ESC arm compared with the ESC-alone arm at 24 months. The most appropriate summary of the results of this trial is that there is no evidence of superiority of SRT over ESC for young people presenting with social withdrawal and non-psychotic severe and complex mental health problems.

On some dimensions there appeared to be mean differences favouring ESC over SRT plus ESC. However, the differences on the primary outcome and the large majority of secondary outcomes did not meet the level for conventional significance, apart from social phobia and some subscales of negative symptoms at 15 months. At 24 months, mean differences favoured ESC over SRT plus ESC on structured activity. Missingness of data was consistently higher in the ESC-alone group than in the SRT plus ESC group, and the bias and total amount of missingness of data increased over time. At 24 months, > 30% of data were missing and there was a bias resulting from the fact that the amount of missingness of data in the ESC-alone group was twice that in the SRT plus ESC group. It is plausible that differential missingness of data could bias results in favour of ESC, particularly at the later assessment stages. We can be clear that there is no superiority of SRT, but, despite trends favouring ESC alone, we should be more cautious in concluding that ESC alone was superior, as most of the results did not reach conventional statistical significance levels and there was a clear bias because of unbalanced levels of missingness of data.

Participants in both arms of the trial made large gains over time from baseline on all measures. There were large effect size gains in structured and constructive economic activity of > 10 hours per week in both arms. This is more than double the 4 hours that constitutes a clinically meaningful difference. There was a > 50% improvement in the rate of participants meeting diagnostic criteria for depression, panic, agoraphobia and social phobia in both groups, and large effect gains in self-reported assessments of depression, social anxiety, hopelessness and schizotypal symptoms of paranoia and anomalous experiences. There were also marked reductions in alcohol and drug use disorders.

The ESC provided in this trial was designed and intended to maximise the delivery and availability of combinations of existing evidence-based interventions to this group of young people with non-psychotic severe and complex mental health problems. Close examination showed the ESC delivered in the trial to be highly active, involving comprehensive individualised packages of care with combinations of medication, evidence-based psychological therapy (including symptom-focused CBT) and social care (including specific employment support). Most participants in the ESC condition received case management support, a majority (in both arms) were taking antidepressant medication, around half had psychological therapy over the course of the trial, and around one-third had comprehensive employment support. The packages of care delivered outside the trial were similar in both arms,

but slightly higher rates of receiving psychological therapy and packages of NHS treatment were recorded in the ESC-only group. What the trial appears to indicate is that the presence of active packages of youth mental health care, including primary care support, antidepressant medication and, where indicated, standard psychological therapy and employment and youth support, is sufficient to make relatively large effect size gains in activity and in mental health symptoms, and that the adjunctive provision of specific intensive SRT adds little to such gains. The results are possibly akin to those of the IMPACT trial[93] on adolescent depression, which showed relative equivalence of the effectiveness of case management in comparison with different types of psychological therapy (psychoanalytical psychotherapy and CBT).

The results are surprising given the evidence base that gave rise to this trial. Previous research has tended to find that patients with severe and complex problems struggle to access and may be relatively unresponsive to existing interventions.[5–8] Furthermore, follow-up studies have suggested that the longer-term outcomes are poor, with social withdrawal in association with non-psychotic severe and complex mental health problems and APS predictive of poor outcomes.[2,3] In contrast, in this trial both the ESC-alone group and the SRT plus ESC groups achieved large effect size gains in structured and constructive economic activity, as assessed by time use, and in mental health symptoms, particularly in hopelessness, anxiety, paranoia and APS, over time and for up to 2 years. It is important to note that ESC in this trial was not treatment as usual. It was an active and comprehensive intensive treatment control condition comprising a combination of evidence-based interventions. As identified in our qualitative participant process evaluations,[70,71] participation in the ESC arm of the trial and in the trial procedures appeared to be an enhanced intervention experience that was beneficial to participants. Future research should perhaps focus on how routine services can maximise the implementation of the optimal combination of existing evidence-based interventions for this often-neglected group of participants.

Strengths and limitations

This trial had many strengths, most notably that it is a large trial involving the recruitment of a very withdrawn population of young people with severe mental illness across diverse regions of the UK and recruited from a wide array of services. This is a difficult-to-research group for whom any consistent evidence of outcomes is difficult to obtain because of problems with non-engagement and retention. Recruitment and retention of this sample is in and of itself an achievement, and the information on outcomes for the cohort provides novel data on a group that is of increasing interest to policy-makers. The further strengths of this study were good internal and external validity for the trial on the primary outcome and on the main secondary outcomes. The study was conducted with a high degree of rigour and retention to the primary outcome was highly satisfactory. All researchers involved in the study received regular supervision and careful routine checks on inter-rater reliability throughout. All outcomes were reliable and completed blind to intervention allocation. SRT was delivered rigorously and thoroughly, with good adherence to the therapy model by a group of highly committed therapists, and was received well by participants.

A limitation of the study was that it was compromised by the level and pattern of missing data in the secondary outcomes, particularly at the 24-month assessment. However, it should be highlighted again that the primary outcome was originally designed to be assessed at 15 months and the 24-month assessment was brought in at a later stage as a specific standalone follow-up study. Although there were missing data, this was not regarded as being to a degree that compromised the use of ITT analyses as specified in the statistical analysis plan for the main study on primary and secondary outcomes at 15 months. The characteristics of the target group in this study, being by definition a difficult-to-engage and extremely withdrawn sample, represent a challenge to researchers, especially where longer-term follow-up assessments are reliant on face-to-face assessments. Notably, in the SUPEREDEN3 trial, which compared SRT plus EIP services with EIP services alone, there was also

differential missingness of data with greater retention in the arm receiving SRT.[40] In the present trial, additional measures were used to improve retention across trial arms, including the provision of participant reimbursement at all assessment points, mid-point telephone contact and provision of a newsletter to participants between follow-up points; yet such measures did not appear to result in equivalent retention for those individuals not receiving SRT. Potentially, future studies in this area might maximise the rate of follow-up by focusing on hard proxy variables of engagement in services, which may be derived from health-care records rather than from face-to-face assessments, especially as engagement is itself an important outcome in this population.

A further limitation of this study was that many of the secondary outcomes have wide CIs (an indication of low statistical power), suggesting low precision or uncertainty in the estimation of treatment effects, which is probably an unavoidable consequence of undertaking research with what is a complex and heterogeneous clinical group with differing symptomatology. Furthermore, the study was, by necessity, single blind, and thus may be affected by the fact that participant were aware of their allocation and whether or not they were receiving the intervention of interest.

In line with good practice recommendations for cost-effectiveness analyses,[94] we concentrated on expected large cost drivers (e.g. health professional visits). A potential limitation is, however, that certain aspects of health care (e.g. medications) were not costed. Similarly, any differences in the loss in productivity, as well as family and carer costs, were also not costed, although, given that the intervention was not estimated to be more effective than standard care, we would not expect there to be a difference in these costs between arms. Thus, the study result would have been expected to be the same, even if a wider cost perspective were adopted.

A further potential limitation is that our analysis is based on evidence from just one trial. However, if an economic model were to be created based on these trial data, then one would not expect the long-term or extrapolated results, for example, to differ from those presented here, as the intervention was not estimated to be effective.

Clinical implications

The assumption that underpinned this study was that young people who are withdrawn and have non-psychotic severe and complex health problems represent a group who are unresponsive to existing interventions and, therefore, may require a dedicated intensive psychosocial intervention. The findings of the study are important in clearly demonstrating that, contrary to prediction, this group can respond well and make clinical and social recovery if a comprehensive range of existing interventions are made available. What is needed is an enhancement of standard care to ensure the provision of the optimal combination of currently available evidence-based interventions. This includes a combination of case management and support with appropriate medication, specific symptom-focused psychological therapy, and employment and youth support. Service user feedback suggests that delivering such services in the context of hope and messages of recovery is key.[95–97] Similarly, both participants and SRT therapists in the present process evaluation emphasised the importance of hopefulness and motivation for this patient group (Briony Gee, Norfolk and Suffolk NHS Trust, 2021, personal communication).[98] The take-away message is not to do nothing; instead, it should be to highlight the need to assist services and frontline clinicians to enhance care delivery for this population and ensure that optimal care pathways are delivered for those most at need. Such care pathways must also recognise the dynamic identity exploration occurring in the those aged 14–25 years[41,42] and the need for developmentally appropriate interventions for this group.

The key clinical and research implication of this study is to examine the optimal ways that services can be provided in such cases. Although the evidence here is that young people with non-psychotic severe and complex mental health problems can and do respond if the right combination of evidence-based

interventions is made available, all too often such interventions are not available in routine services. The factors associated with effective delivery and implementation of the optimal combinations of interventions to this often-neglected group of young people are complex. One issue is resources and it should be noted that the present trial was conducted in services that already had a specific focus on youth mental health and the provision of interventions to young people with complex needs. In these services, an optimal combination of evidence-based interventions was available and was delivered to participants in the trial. Not all services in the NHS, let alone those in less well-resourced health-care settings, have such resources available. The present trial provides support for the provision of comprehensive youth mental health services that can offer a full range of medical, psychological and psychosocial interventions. Moreover, even where resources are available, implementation and delivery of care can be complex, as, young people may need help to be detected, to engage with services and to continue with interventions. Sometimes these young people can fall between the gap of services; for example, some of our participants had previous experience of being regarded as not having sufficiently severe symptoms to meet the criteria for EIP services, but, at the same time, their symptoms were deemed to be too severe or they were considered incapable of engaging with services for treatments to address common mental health problems. Others fall into gaps between child and adult services. This study suggests that good outcomes are possible by systematic provision of currently available evidence-based interventions. The results of this study are encouraging to all clinicians to do what is possible with the range of existing interventions to deliver optimal packages of care. If delivered in a spirit of hope for realistic recovery, good outcomes can be expected.

The qualitative research suggested that the trial procedures themselves provided a focus for optimal detection and delivery of interventions, including ESC. Possible ways to replicate such procedures to organise and implement detection and delivery of care to high-risk groups that may not otherwise engage in routine practice might be possible in more dedicated youth mental health services. These services offer open-door youth-oriented engagement and assertive case management to ensure that combinations of existing evidence-based interventions are delivered to those who need them. The qualitative research also revealed that hopelessness can potentially lead to non-engagement and lack of implementation of interventions, both within the young person and by staff who treat them, who can become overwhelmed by the complexity of clinical presentations. The results of this study, again, provide hope in suggesting that, despite initially highly complex and very severe presentations and extreme withdrawal over a period of 15 months to 2 years, many young people with complex and severe mental health and social problems improve significantly. We cannot be absolutely certain that it was the systematic detection and delivery of the right combination of existing evidence-based interventions that facilitated this; it is possible that some participants made natural recoveries. Given the chronicity, severity and complexity of problems at baseline, it seems probable that the enhancement of standard care and the systematic provision of evidence-based interventions according to need in both arms played a role in promoting recovery.

In conclusion, clinicians should be supported in their attempts to manage more complex clients with clear hope that systematic delivery of the right combination of existing interventions based on needs can be effective. Support and training to give clinicians confidence to manage such cases may also be warranted. The structure offered by the recruitment and assessment processes in this trial possibly provides systematic ways in which routine services can identify cases and offer hopefulness through a structured assessment of needs and feedback to clinicians.

Implications for detection

The evidence underpinning this study was that young people with premorbid social decline and non-psychotic severe and complex mental health problems have the poorest social outcomes, and that complex and severe psychopathology further predicts poor response to existing interventions.[4,47,99–103] This remains a good summary of the literature. How can we reconcile this evidence with the outcomes in this study that such young people appear to respond with large effect gains from the provision of ESC? What are the implications for detection and intervention? The first is that the choice of these

factors (a combination of social disability and complex severe psychopathology) lacked specificity as a detection criterion; these are generic indicators. Poor social outcome is common, as is complexity in youth mental health presentations.[4,100,104]

Perhaps, despite this being a combination of risk factors that are known to be associated with poor outcome, the lack of specificity and high prevalence of this presentation may result in false detection of a group at purportedly high risk. Although there is an association with poor outcome, many of these young people in fact have a good outcome, if good services are provided. It might be that this population includes a group that have a good natural course of recovery; young people are at a time of their lives when obtaining work, leaving the family home, starting higher education, or gaining a partner or friend can have a major effect in social and symptomatic presentations.

Similarly, in intervention studies, although there is an association of likelihood of poor response to specific interventions, clearly there is reserve response capacity, particularly if the service response is hopeful, wide-reaching and systematic. It is noteworthy that the service offered to this group in ESC did not reflect a single intervention, but typically involved combinations of case management, medication, psychological therapy, and employment and personal youth support. The key take-away message is that the presence of what appear to be poor prognostic factors and complexity should not lead to an assumption of non-responsiveness. Many young people can and do respond if packages of care are offered.

Finally, although the evidence from this study suggests that the present approach to high-intensive SRT is not needed, it is possible that other interventions may have a better effect. Another approach possibly worth investigating is stepped care to identify cases that do not respond to enhanced standard packages of care. In a previous study,[40] the provision of SRT for young people with early psychosis was delivered only once there was no evidence of response to EIS after at least 1 year. In that study, there was clear evidence for a specific benefit of SRT.[40] In the present study, although some participants had previously been offered and had engaged with packages of care, for others SRT was provided at initial presentation to services (albeit with all participants showing evidence of at least 6 months of persistent social decline). It is possible that more specific high-intensity therapy may be best reserved for cases showing treatment resistance, perhaps after clearly being offered existing interventions for longer periods. A stepped care approach may be warranted for cases that do not respond to ESC interventions.

Further research

Capture engagement as an outcome of intervention

The differential missingness of data according to intervention allocation is notable. Although there appears to be no superiority of SRT according to the between-group data comparisons, this differential missingness of data does suggest that SRT has a clear effect on engagement. Engagement itself is an important predictor of outcome and target for intervention. Of those young people with ARMS or who have transitioned to a first episode of psychosis, approximately one in three or four young people will disengage from early intervention services.[105] Future research that evaluates SRT as a predictor of treatment and broader service engagement and patterns of continued engagement over time would be worthwhile. Furthermore, such research could explore the putative mechanisms of increased engagement and endeavour to isolate the key components of SRT that have impact.

Capture outcomes in absentia

In a population of especially withdrawn young people, the identification and operationalisation of meaningful outcomes that can be measured in the absence of face-to-face assessment would be a worthy goal. New technologies could offer a potential solution as, for example, smartphones have a high level of use among young people and could provide the means to capture behavioural data, with participant permission.

Investigating person-centred treatment for young people with emerging non-psychotic severe and complex mental health problems

The large effects in both trial conditions suggest that both ESC alone and SRT plus ESC are associated with meaningful gains across broad spectra of functioning and symptom outcomes. Nevertheless, particularly considering the substantial minority of ESC participants who dropped out of the trial, there is a need to explore what works best for whom. It is very possible that within the trial population there existed subgroups of young people for whom only certain, specific ESC and/or SRT components were necessary and sufficient. Such components may include technical, logistical and relational elements of the health-care interaction.[95] The identification of these components, using both quantitative and qualitative methods, has important clinical and economic implications for service design and delivery in the treatment of young people with emerging non-psychotic severe and complex mental health problems. Moreover, this report presents the average group-level changes and does not constitute an investigation of variation in responsiveness to either trial arm. The identification of possible subgroups of young people without psychosis, but with emerging non-psychotic severe and complex mental health problems and social disability, who may constitute a population likely to be 'treatment resistant' and, thus, in need of a high-intensity, specialised or social recovery intervention, would be a worthy endeavour.

Conclusions

The rationale for the trial emphasised the need for detection and intervention as it had been commonly highlighted that cases of young people with non-psychotic severe and complex mental health problems tended to be neglected by services. Even though these young people often seek treatment, they were identified as falling between gaps in services and being regarded as difficult to engage and manage. This study did not find evidence for the superiority of SRT when delivered as an adjunctive to enhanced treatment as usual. This study showed that it is possible to successfully detect, recruit and retain young people with severe and complex mental health difficulties and social withdrawal into a psychological treatment trial of this type. The participants recruited demonstrated very severe withdrawal, with a mean of 11 hours per week activity compared with a population mean of > 60 hours per week for young people in the same age group;[47] this was accompanied by very severe levels of depression, social anxiety, hopelessness and the presence of APS.

The study shows that it is possible for standard services to deliver enhanced packages of care to this group if resources are available and suggests that these packages can be effective. The results provide support for and are consistent with lobbying for generic youth mental health services that seek to engage young people. The results of the present study show that, in terms of interventions, offering the range of existing services available within the NHS (case management, medication, symptom-focused CBT, and employment and youth-focused support) is sufficient to obtain a clinically important effect and that a more focused, intensive and specific psychological intervention, such as SRT, may not be needed. SRT was also not estimated to be cost-effective. Potentially, it may be only young people with psychosis who need a more intensive specialist intervention and for whom interventions such as SRT show a specific effect in enhancing standard care.[40] The clinical implications of the study are therefore significant in emphasising the importance of mental health services to identify, engage and treat the types of non-psychotic severe and complex mental health problems targeted in this trial using their existing repertoire of interventions, with the confidence of obtaining good outcomes even if the initial presentations can appear somewhat intransigent, and indeed complex and overwhelming.

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Contributions of authors

Professor David Fowler (https://orcid.org/0000-0001-5806-2659) planned the funding applications for the internal pilot and extension phase of the trial. Professor Fowler led the design of the trial, and the development of the protocol and statistical analysis plan. Professor Fowler led the trial as the Chief Investigator with Professor Paul French. Professor Fowler wrote the final report with Dr Clio Berry.

Dr Clio Berry (https://orcid.org/0000-0003-1164-9836) made a substantial contribution to the development of the trial protocol and statistical analysis plan. Dr Berry managed the trial as the trial manager (extension phase): managing the delivery of the trial, ensuring the implementation of the protocol and associated amendments, supervising and training research staff, supervising and co-ordinating recruitment, and managed the trial data, including data entry and quality appraisal, with support from NCTU. Dr Berry prepared the final data set for analysis. Dr Berry made substantial contributions to the design, delivery and analysis of the process evaluation involving research therapists. Dr Berry wrote the final report with Professor Fowler.

Dr Joanne Hodgekins (https://orcid.org/0000-0003-4124-854X) made substantial contributions to the applications for funding, design of the trial and development of the protocol. Dr Hodgekins led the trial in the East Anglia site as Principal Investigator with Dr Jon Wilson. Dr Hodgekins provided expert training and supervision for all trial staff in the assessment of time use. Dr Hodgekins made substantial contributions to the design, delivery and analysis of the process evaluations involving young people. Dr Hodgekins provided trial therapy, supervised research and therapy staff, and contributed to trial management oversight. Dr Hodgekins made substantial contributions to and critically read the final report.

Professor Robin Banerjee (https://orcid.org/0000-0002-4994-3611) made contributions to the funding applications. Professor Banerjee contributed to the design and development of the trial protocol. Professor Banerjee made substantial contributions to the development and delivery of protocol amendments. Professor Banerjee contributed to trial management oversight. Professor Banerjee made contributions to and critically read the final report.

Dr Garry Barton (https://orcid.org/0000-0001-9040-011X) was the health economist. Dr Barton made contributions to the funding applications. Dr Barton made substantial contribution to the development of the trial protocol and statistical analysis plan. Dr Barton conducted the health economic analysis and made substantial contributions to and critically read the final report.

Dr Rory Byrne was the lead for PPI. Dr Byrne made contributions to the funding applications. Dr Byrne made substantial contributions to the design of the trial and development of the protocol. Dr Byrne led the PPI activity with the PAT. Dr Byrne made substantial contributions to the design, delivery and analysis of the process evaluations involving young people. Dr Byrne made substantial contributions to the design of patient-facing materials used in the delivery of the trial. Dr Byrne contributed to trial management oversight. Dr Byrne critically read the final report.

Dr Timothy Clarke made substantial contributions to the applications for funding, design of the trial and development of the protocol. Dr Clarke led the trial as the trial manager (internal pilot phase): managing the delivery of the trial, ensuring the implementation of the protocol and associated amendments, supervising and training research staff, supervising and co-ordinating recruitment, delivering therapy and supervising research therapists, and working with NCTU to set up the trial database. Dr Clarke made substantial contributions to the design, delivery and analysis of the process evaluations involving young people. Dr Clarke made substantial contributions to and critically read the final report.

Dr Rick Fraser made contributions to the funding applications, and the design and development of the trial protocol. Dr Fraser was the Principal Investigator for the Sussex site. Dr Fraser contributed to trial management oversight. Dr Fraser critically read the final report.

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Dr Sophie Parker (https://orcid.org/0000-0001-5596-7524) made substantial contributions to the applications for funding, design of the trial and development of the protocol. Dr Parker provided site co-ordination in Greater Manchester, including supervision of research staff and co-ordination of recruitment. Dr Parker provided expert supervision and training for all trial staff in ARMS and diagnostic interview assessment. Dr Parker contributed to trial management oversight. Dr Parker made substantial contributions to and critically read the final report.

Professor Lee Shepstone was the trial statistician. Professor Shepstone made contributions to the funding applications. Professor Shepstone made a substantial contribution to the development of the trial protocol and statistical analysis plan. Professor Shepstone led the statistical analysis, which was conducted with Dr Kelly Grant. Professor Shepstone made substantial contributions to and critically read the final report.

Dr Jon Wilson (https://orcid.org/0000-0002-5279-6237) made substantial contributions to the funding applications, design of the trial and development of the protocol. Dr Wilson was the Co-Principal Investigator for the East Anglia site with Dr Hodgekins. Dr Wilson contributed to trial management oversight.

Professor Paul French made leading contributions to the applications for funding, design of the trial and development of the protocol. Professor French led the trial as Co-Chief Investigator with Professor Fowler and was the Principal Investigator for the Greater Manchester site. Professor French provided training and supervision to research and therapy staff. Professor French made substantial contributions to and critically read the final report.

Publications

Trial protocol

Fowler D, French P, Banerjee R, Barton G, Berry C, Byrne R, *et al.* Prevention and treatment of long-term social disability amongst young people with emerging severe mental illness with social recovery therapy (the PRODIGY trial): study protocol for a randomised controlled trial. *Trials* 2017;**18**:315.

Process evaluation

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Sacadura C. *Social Recovery Therapy: An Interpretative Phenomenological Analysis of Therapists' Experience of Hope Working with Complex Clients*. Doctoral Thesis. Leicester: University of Leicester; 2018.

Data-sharing statement

We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. Further information regarding SRT and associated research is available at: www.socialrecoverytherapy.co.uk.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Changes to protocol

TABLE 37 Amendments to study protocol

		Amendment			
Phase	**Protocol version**	**Number**	**Classification**	**Date**	**Details**
Internal pilot		Amendment 1	Substantial	20 December 2012	1. Addition of participant crisis cards 2. Amendment to assessment battery 3. Amendment to provide assessment summary feedback to participants 4. Addition of recruitment posters and leaflets
		Amendment 2	Minor	1 February 2013	Addition of new Participant Identification Centres
		Amendment 3	Minor	19 February 2013	Addition of new logos to study documents
		Amendment 4	Minor	1 May 2013	Addition of new research sites within existing centres
		Amendment 5	Minor	5 March 2014	Principal Investigator activity delegation. Addition of thank-you cards to participants at trial exit. Modification to mid-point contact procedures
		Amendment 6	Substantial	19 January 2015	1. Addition of the 24-month follow-up assessment 2. Extension of qualitative substudy
		Amendment 7	Minor	27 April 2017	Extension of trial end date to May 2019 in the light of extended recruitment period in the recruitment extension phase to reach target of 270 participants across the trial
Extension	V1.0 29 June 2015	Amendment 1.1	Minor	26 February 2016	Clarification that inclusion criterion 2 (active positive psychotic symptoms or history of FEP) referred to presence of psychosis as operationalised symptomatically or as according to therapeutic antipsychotic medication (or both)
	V2.0 29 January 2016	Amendment 2.0	Substantial	2 February 2016	1. Addition of GP practices as Patient Identification Centres 2. Amendment to PIS (V3, 29 September 2015) and consent form (V3, 29 September 2015) to clarify mandatory vs. optional consent items 3. Amendment to PIS and consent form to clarify arrangements regarding possible information-sharing with school professionals as applicable

continued

TABLE 37 Amendments to study protocol (*continued*)

Phase	Protocol version	Amendment			
		Number	Classification	Date	Details
					4. Addition of template letter to use to inform GPs and referrers (V1, 26 November 2015) of 'screen fails' 5. Correction to trial protocol (V2.0, 29 January 2016) to clarify insurance and indemnity arrangements and to clarify that paper assessment packs (i.e. 'source data') are retained at site
	V2.0 29 January 2016	Amendment 2.1	Substantial	1 April 2016	Addition of new leaflet to support GP recruitment (V2, 23 March 2016)
	V2.0 29 January 2016	Amendment 2.2	Minor	24 November 2016	Continuation of recruitment beyond planned end date of November 2016 to reach target of 270 participants across the trial
	V3.0 27 July 2017	Amendment 3.0	Substantial	1 September 2017	1. Amendment to trial protocol (V3.0, 27 July 2017) to include additional PIS (A3.0 V1 27 July 2017) and consent form (A3.0 V1, 27 July 2017) to allow collection of participant national pupil data 2. Amendment to trial protocol (V3.0, 27 July 2017) to add Premorbid Adjustment Scale (Cannon-Spoor *et al.*, 1982[106]) as an additional measure at the 24-month follow-up assessment 3. Addition of subprotocol describing research therapist qualitative substudy (TECH V1, 16 August 2017) with associated PIS (V2, 1 September 2017) and consent form (V1, 16 August 2017)
	V4.0 13 February 2018	Amendment 4.0	Substantial	6 April 2018	1. Removal of Premorbid Adjustment Scale (Cannon-Spoor *et al.*, 1982[106]) as an additional measure at the 24-month follow-up assessment 2. Addition of online consent form (A4.0 V1, 4 April 2018) to allow online consent provision for collection of participant national pupil data

Note
The internal pilot phase and the extension phase, although reflecting the same registered trial (ISRCTN47998710), were subject to two separate research governance and ethics approval processes.

Appendix 2 Supplementary figures

TABLE 38 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) – schedule of enrolment, interventions and assessments

	Study period						
	Enrolment			Post allocation			Close out
PRODIGY	Screening	Baseline	Allocation	Intervention (months)	Follow-up (months)		Follow-up (months)
Time point	$-t_1$[a]	$-t_2$[a,b]	0	9	9	15	24
Enrolment							
Informed consent	✗						
Eligibility screen	✗						
Randomisation			✗				
Interventions							
SRT + ESC			◆———	———			
ESC alone			◆———	———			
Assessments							
Primary outcome							
TUS[c]	✗				✗	✗	✗
Secondary mental health outcomes							
GAF[c]	✗				✗	✗	✗
CAARMS[c]	✗				✗	✗	✗
SANS		✗			✗	✗	✗
SCID		✗			✗	✗	✗
SIAS		✗			✗	✗	✗
BDI-II		✗			✗	✗	✗
Health economic outcomes							
HSRUQ		✗			✗	✗	✗
EQ-5D		✗			✗	✗	✗
Hypothesised mediators							
AAQ-II		✗			✗	✗	✗
MLQ		✗			✗	✗	✗
THS		✗			✗	✗	✗
SSI		✗			✗	✗	✗
BCSS		✗			✗	✗	✗
Hypothesised moderators							
Logical Memory I		✗				✗	
COWAT		✗				✗	

continued

TABLE 38 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) – schedule of enrolment, interventions and assessments (*continued*)

	Study period						
	Enrolment			Post allocation			Close out
PRODIGY	Screening	Baseline	Allocation	Intervention (months)	Follow-up (months)		Follow-up (months)
Other outcomes							
AUDIT		✗			✗	✗	✗
DUDIT		✗			✗	✗	✗
BHS		✗			✗	✗	✗
AEs			✗	✗	✗	✗	✗

AAQ-II, Acceptance and Avoidance Questionnaire II; BCSS, Brief Core Schema Scales; BDI-II, Beck Depression Inventory-II; HSRUQ, Health Service Resource Use Questionnaire; MLQ, Meaning in Life Questionnaire; THS, Trait Hope Scale.

a $-t_1$: once eligibility had been confirmed, a date ($-t_2$) was arranged with the participant to complete the remaining assessments. Once remaining assessments were completed, treatment allocation was performed.

b $-t_2$: remaining assessments were completed as soon as possible after confirmation of eligibility; however, no restrictions were placed on the number of visits over which these were completed. This allowed participants to complete the assessments at their own pace and according to their own availability.

c TUS, GAF and CAARMS were administered as part of the eligibility screen. TUS then formed the primary outcome, with the primary end point at 15 months. GAF and CAARMS formed secondary mental health outcomes.

Appendix 3 Supplementary statistical analysis tables

Analysis of secondary time use outcomes

TABLE 39 Secondary time use outcomes: analysis of PP population at 9 and 15 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
9 months						
Constructive economic activity (hours per week)	14.0 (11.8)	16.6 (15.9)	−1.36 (−5.14 to 2.42)	0.48	0.03 (−0.23 to 0.29)	0.804
Missing, *n*	4	17				
Total hours paid employment[d]	99.8 (311.3)	283.9 (511.4)	−157.12 (−292.33 to −21.91)	0.023	−1.00 (−1.86 to −0.14)	0.023
Missing, *n*	11	48				
Total hours education[d]	134.5 (367.6)	108.0 (235.0)	36.07 (−64.20 to 136.34)	0.48	0.22 (−0.61 to 1.04)	0.602
Missing, *n*	13	50				
Total hours voluntary employment[d]	53.2 (244.5)	50.7 (170.9)	−2.38 (−70.81 to 66.06)	0.95	−0.02 (−0.70 to 0.66)	0.96
Missing, *n*	19	47				
Total hours all activity[d]	291.8 (499.4)	454.2 (592.9)	−107.46 (−283.94 to 69.01)	0.23	−0.42 (−1.30 to 0.46)	0.35
Missing, *n*	19	56				
15 months						
Constructive economic activity (hours per week)	13.3 (13.2)	22.0 (24.5)	−6.92 (−12.72 to −1.12)	0.020	−0.28 (−0.56 to −0.00)	0.049
Missing, *n*	4	24				
Total hours paid employment[d]	41.3 (110.2)	123.6 (275.2)	−73.89 (−139.23 to −8.55)	0.027	−0.58 (−1.25 to 0.10)	0.095
Missing, *n*	11	31				
Total hours education[d]	54.0 (137.4)	88.8 (176.3)	−34.56 (−83.38 to 14.26)	0.16	−0.33 (−1.03 to 0.37)	0.35
Missing, *n*	13	31				
Total hours voluntary employment[d]	17.1 (41.2)	36.8 (96.3)	−16.58 (−40.21 to 7.04)	0.17	−0.03 (−0.60 to 0.54)	0.92
Missing, *n*	15	28				

continued

TABLE 39 Secondary time use outcomes: analysis of PP population at 9 and 15 months (*continued*)

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Total hours all activity[d]	113.0 (170.3)	258.8 (359.8)	−134.51 (−224.41 to −44.60)	0.004	−0.52 (−1.28 to 0.24)	0.18
Missing, *n*	19	35				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Analysis of general psychopathology diagnoses continued

TABLE 40 The CAARMS transition secondary outcomes at 9 and 15 months

CAARMS transition	Allocation arm, *n* (%)		Odds ratio[a] (95% CI[b])	*p*-value[c]
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Transition to psychosis at 9 months	12 (9.8)	8 (7.5)	1.30 (0.49 to 3.44)	0.59
Missing, *n*	16	25		
Transition to psychosis at 15 months	6 (5.6)	1 (1.1)	7.33 (0.71 to 76.25)	0.095
Missing, *n*	30	44		

a Logistic regression model, includes stratification variables and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), gives odds ratio of transition (odds of transition for the intervention group are the given result, number of times greater, than the odds of transition for the control group).
b 95% Wald CIs.
c The *p*-value is based on a null hypothesis of zero effect.

TABLE 41 The CAARMS transition secondary outcomes at 24 months

CAARMS transition	Allocation arm, *n* (%)		Odds ratio[a] (95% CI[b])	*p*-value[c]
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Transition to psychosis at 24 months	3 (3.1)	2 (2.5)	1.29 (0.20 to 8.19)	0.79
Missing, *n*	40	51		

a Logistic regression model, includes stratification variables and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), gives odds ratio of transition (odds of transition for the intervention group are the given result, number of times greater, than the odds of transition for the control group).
b 95% Wald CIs.
c The *p*-value is based on a null hypothesis of zero effect.

TABLE 42 The SCID diagnoses (1) mood outcomes at 9 and 15 months further data

Mood outcome	Time point	Prevalence, *n* (%), *n* missing		Relative risk[a] (95% CI[b])	*p*-value[c]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Past major depressive episode	Baseline	33 (23.9), 0	41 (31.1), 0		
	9 months	53 (42.4), 13	36 (32.1), 20	1.32 (0.94 to 1.85)	0.109
	15 months	33 (27.1), 16	25 (25.0), 32	1.08 (0.69 to 1.69)	0.76
Past mania	Baseline	2 (1.5), 0	5 (3.8), 0		
	9 months	2 (1.6), 13	3 (2.7), 20	0.60 (0.10 to 3.51)	0.67
	15 months	1 (0.8), 16	2 (2.0), 30	0.42 (0.04 to 4.54)	0.59
Past hypomania	Baseline	2 (1.5), 0	1 (0.8), 0		
	9 months	2 (1.6), 13	3 (2.7), 20	0.60 (0.10 to 3.51)	0.67
	15 months	4 (3.3), 16	2 (2.0), 30	1.67 (0.31 to 8.94)	0.69
Major depressive disorder	Baseline	95 (68.8), 0	93 (70.5), 0		
	9 months	66 (52.8), 13	55 (49.6), 21	1.07 (0.83 to 1.37)	0.70
	15 months	58 (47.5), 16	43 (42.2), 30	1.13 (0.84 to 1.51)	0.50

a A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
b Asymptotic Wald 95% confidence limits.
c The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

TABLE 43 The SCID diagnoses (2) anxiety, eating and somatoform outcomes at 9 and 15 months further data

Anxiety, eating and somatoform outcome	Time point	Prevalence, *n* (%), *n* missing[a]		Relative risk[b] (95% CI[c])	*p*-value[d]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Panic disorder	Baseline	6 (4.4), 0	6 (4.6), 1		
	9 months	4 (80.0), 1	3 (50.0), 0	1.60 (0.64 to 3.98)	0.55
	15 months	1 (25.0), 2	2 (40.0), 1	0.63 (0.08 to 4.66)	1.00
Hypochondriasis	Baseline	4 (2.9), 0	3 (2.3), 0		
	9 months	2 (50.0), 0	2 (66.7), 0	0.75 (0.21 to 2.66)	1.00
	15 months	3 (75.0), 0	1 (33.3), 0	2.25 (0.41 to 12.28)	0.47
Anorexia nervosa	Baseline	1 (0.7), 0	1 (0.8), 0		
	9 months	0 (0), 0	0 (0), 0	–	
	15 months	0 (0), 0	0 (0), 0	–	
Bulimia nervosa	Baseline	1 (0.7), 0	0 (0), 0		
	9 months	0 (0), 1	0 (0), 0	–	
	15 months	0 (0), 1	0 (0), 0	–	

continued

TABLE 43 The SCID diagnoses (2) anxiety, eating and somatoform outcomes at 9 and 15 months further data (*continued*)

Anxiety, eating and somatoform outcome	Time point	Prevalence, *n* (%), *n* missing[a]		Relative risk[b] (95% CI[c])	*p*-value[d]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Binge-eating disorder	Baseline	2 (1.5), 0	1 (0.8), 0		
	9 months	1 (50.0), 0	0 (0), 0	–	1.00
	15 months	1 (50.0), 0	0 (0), 0	–	1.00
Anxiety disorder NOS	Baseline	4 (2.9), 0	3 (2.3), 0		
	9 months	1 (25.0), 0	2 (100), 1	0.25 (0.05 to 1.36)	0.40
	15 months	1 (25.0), 0	1 (50.0), 1	0.50 (0.06 to 4.47)	1.00

NOS, not otherwise specified.
a For category (2) variables, baseline prevalence is based on the total number (*N*) within the relevant group. For 9 months, 15 months and 24 months, for each diagnosis, the prevalence is based on the total number at baseline with a positive diagnosis (discounting 'missing' or negative diagnosis at baseline).
b A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
c Asymptotic Wald 95% confidence limits.
d The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

TABLE 44 The SCID diagnoses (1) mood outcomes at 24 months further data

Mood outcome	Time point	Prevalence, *n* (%), *n* missing		Relative risk[a] (95% CI[b])	*p*-value[c]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Past major depressive episode	Baseline	33 (23.9), 0	41 (31.1), 0		
	24 months	24 (22.6), 32	12 (14.6), 50	1.55 (0.82 to 2.91)	0.19
Past mania	Baseline	2 (1.5), 0	5 (3.8), 0		
	24 months	2 (1.9), 32	1 (1.2), 49	1.57 (0.14 to 16.98)	1.00
Past hypomania	Baseline	2 (1.5), 0	1 (0.8), 0		
	24 months	2 (1.9), 32	2 (2.4), 49	0.78 (0.11 to 5.44)	1.00
Major depressive disorder	Baseline	95 (68.8), 0	93 (70.5), 0		
	24 months	45 (42.5), 32	28 (33.7), 49	1.26 (0.87 to 1.83)	0.23

a A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
b Asymptotic Wald 95% confidence limits.
c The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

TABLE 45 The SCID diagnoses (2) anxiety, eating and somatoform outcomes at 24 months further data

Anxiety, eating and somatoform outcome	Time point	Prevalence, *n* (%), *n* missing[a]		Relative risk[b] (95% CI[c])	*p*-value[d]
		SRT + ESC (*N* = 138)	ESC alone (*N* = 132)		
Panic disorder	Baseline	6 (4.4), 0	6 (4.6), 1		
	24 months	0 (0), 2	3 (60.0), 1		0.17
Specific phobia	Baseline	10 (7.3), 0	4 (3.0), 0		
	24 months	4 (57.1), 3	1 (33.3), 1	1.71 (0.31 to 9.61)	1.00
Hypochondriasis	Baseline	4 (2.9), 0	3 (2.3), 0		
	24 months	3 (100), 1	0 (0), 1	–	0.10
Anorexia nervosa	Baseline	1 (0.7), 0	1 (0.8), 0		
	24 months	0 (0), 0	0 (0), 0	–	
Bulimia nervosa	Baseline	1 (0.7), 0	0 (0), 0		
	24 months	0 (0), 1	0 (0), 0	–	
Binge-eating disorder	Baseline	2 (1.5), 0	1 (0.8), 0		
	24 months	1 (50.0), 0	1 (100), 0	0.50 (0.13 to 2.00)	1.00
Anxiety disorder NOS	Baseline	4 (2.9), 0	3 (2.3), 0		
	24 months	1 (25.0), 0	0 (0), 2	–	1.00

NOS, not otherwise specified.
a For category (2) variables, baseline prevalence is based on the total number (*N*) within the relevant group. For 9, 15 and 24 months, for each diagnosis, the prevalence is based on the total number at baseline with a positive diagnosis (discounting 'missing' or negative diagnosis at baseline).
b A relative risk > 1 indicates that the probability of a positive diagnosis is greater in the control group. A relative risk < 1 suggests a greater probability of a positive diagnosis in the intervention group.
c Asymptotic Wald 95% confidence limits.
d The *p*-value of the Fisher's exact test is based on the null hypothesis of no association between groups.

Analysis of negative symptoms

TABLE 46 Scale for the Assessment of Negative Symptoms at baseline

Symptom	Allocation arm, mean (SD)	
	SRT + ESC (*n* = 138)	ESC alone (*n* = 132)
Unchanging facial expression[a]	1.1 (1.5)	0.9 (1.3)
Decreased spontaneous movement	0.6 (1.1)	0.6 (1.0)
Paucity of expressive gestures	1.1 (1.5)	0.8 (1.4)
Poor eye contact	1.2 (1.4)	0.9 (1.2)
Affective non-responsivity	0.7 (1.2)	0.5 (1.0)
Lack of vocal inflections	1.2 (1.5)	0.8 (1.2)
Global rating of affective flat	1.2 (1.4)	0.9 (1.1)
Inappropriate affect	0.3 (0.7)	0.4 (0.8)
Poverty of speech	0.9 (1.4)	0.8 (1.2)
Poverty of content of speech	0.5 (1.1)	0.5 (1.0)
Blocking	0.3 (0.9)	0.3 (0.7)

continued

TABLE 46 Scale for the Assessment of Negative Symptoms at baseline (*continued*)

Symptom	Allocation arm, mean (SD)	
	SRT + ESC ($n = 138$)	ESC alone ($n = 132$)
Increased latency of response	0.7 (1.1)	0.5 (1.0)
Global rating of alogia	0.8 (1.0)	0.7 (0.9)
Grooming and hygiene	1.0 (1.2)	0.9 (1.1)
Impersistence at work or school	4.1 (1.2)	4.2 (1.2)
Physical anergia	3.1 (1.4)	3.3 (1.4)
Global rating of avolition apathy	3.2 (1.1)	3.3 (1.0)
Recreational interest and activity	2.8 (1.4)	2.9 (1.4)
Sexual interest and activity[a,b]	1.5 (1.9)	1.7 (1.9)
Ability to feel intimacy and closeness[a]	1.8 (1.7)	1.8 (1.6)
Relationships with friends and peers	3.1 (1.5)	2.9 (1.5)
Global rating of anhedonia asociality[a]	2.9 (1.2)	2.8 (1.1)
Social inattentiveness	0.6 (1.1)	0.8 (1.3)
Inattentiveness during mental state testing[c]	0.9 (1.4)	0.9 (1.3)
Global rating of attention[c]	0.8 (1.0)	0.9 (0.9)

a This variable has one missing value at baseline for the intervention group.
b This variable has three missing values at baseline for the standard care group.
c This variable has one missing value at baseline for the standard care group.

TABLE 47 Scale for the Assessment of Negative Symptoms outcomes at 9 months

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Unchanging facial expression	0.8 (1.2), 22	0.6 (1.1), 29	0.16 (−0.12 to 0.45)	0.26	0.09 (−0.05 to 0.22)	0.201
Decreased spontaneous movement	0.5 (0.9), 21	0.3 (0.9), 29	0.08 (−0.12 to 0.29)	0.44	0.06 (−0.04 to 0.16)	0.27
Paucity of expressive gestures	0.8 (1.4), 21	0.5 (0.9), 29	0.24 (−0.03 to 0.50)	0.079	0.08 (−0.04 to 0.20)	0.17
Poor eye contact	1.1 (1.4), 21	0.8 (1.1), 29	0.14 (−0.13 to 0.40)	0.307	0.04 (−0.08 to 0.16)	0.53
Affective non-responsivity	0.4 (0.9), 20	0.3 (0.6), 29	0.09 (−0.11 to 0.29)	0.36	0.03 (−0.07 to 0.14)	0.52
Lack of vocal inflections	0.8 (1.2), 18	0.5 (0.9), 29	0.13 (−0.13 to 0.38)	0.33	0.05 (−0.07 to 0.17)	0.408
Global rating of affective flat	0.9 (1.1), 22	0.7 (0.9), 29	0.11 (−0.12 to 0.35)	0.33	0.05 (−0.07 to 0.16)	0.43
Inappropriate affect	0.3 (0.7), 20	0.3 (0.6), 30	0.02 (−0.14 to 0.17)	0.82	0.01 (−0.08 to 0.09)	0.909
Poverty of speech	0.8 (1.3), 18	0.5 (1.0), 28	0.21 (−0.04 to 0.46)	0.099	0.10 (−0.01 to 0.21)	0.084
Poverty of content of speech	0.3 (0.7), 18	0.4 (0.9), 28	−0.09 (−0.30 to 0.12)	0.401	−0.04 (−0.14 to 0.07)	0.503

TABLE 47 Scale for the Assessment of Negative Symptoms outcomes at 9 months (*continued*)

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Blocking	0.3 (0.7), 18	0.3 (0.7), 28	−0.02 (−0.19 to 0.16)	0.87	−0.00 (−0.10 to 0.09)	0.95
Increased latency of response	0.5 (1.0), 18	0.3 (0.7), 28	0.09 (−0.11 to 0.30)	0.38	0.04 (−0.06 to 0.15)	0.43
Global rating of alogia	0.7 (0.9), 18	0.5 (0.8), 28	0.15 (−0.06 to 0.37)	0.16	0.07 (−0.04 to 0.19)	0.21

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

TABLE 48 Scale for the Assessment of Negative Symptoms outcomes at 9 months further data

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Grooming and hygiene	0.8 (1.1), 18	0.7 (1.0), 28	−0.00 (−0.25 to 0.24)	0.98	−0.01 (−0.13 to 0.11)	0.85
Impersistence at work or school	2.9 (2.0), 18	3.0 (2.0), 28	−0.03 (−0.50 to 0.43)	0.89	−0.03 (−0.19 to 0.13)	0.68
Physical anergia	2.1 (1.6), 18	2.4 (1.7), 30	−0.23 (−0.62 to 0.16)	0.25		
Global rating of avolition apathy	2.3 (1.5), 18	2.5 (1.5), 30	−0.10 (−0.44 to 0.24)	0.58		
Recreational interest and activity	1.4 (1.7), 18	1.4 (1.6), 30	0.04 (−0.37 to 0.45)	0.83	−0.01 (−0.18 to 0.17)	0.95
Sexual interest and activity	0.9 (1.5), 21	1.0 (1.6), 32	−0.15 (−0.56 to 0.25)	0.456	−0.06 (−0.23 to 0.11)	0.46
Ability to feel intimacy and closeness	1.0 (1.4), 18	1.1 (1.3), 29	−0.11 (−0.46 to 0.25)	0.56	−0.08 (−0.23 to 0.08)	0.33
Relationships with friends and peers	1.8 (1.7), 18	1.8 (1.7), 29	−0.07 (−0.48 to 0.34)	0.74	−0.01 (−0.17 to 0.15)	0.87
Global rating of anhedonia asociality	1.7 (1.4), 19	1.8 (1.4), 30	−0.14 (−0.49 to 0.21)	0.43		
Social inattentiveness	0.3 (0.8), 22	0.6 (1.1), 29	−0.17 (−0.42 to 0.08)	0.18	−0.07 (−0.19 to 0.05)	0.26
Inattentiveness during mental state testing	0.7 (1.1), 20	0.8 (1.2), 32	0.04 (−0.24 to 0.31)	0.79	0.02 (−0.11 to 0.15)	0.733
Global rating of attention	0.6 (0.9), 23	0.7 (1.0), 31	−0.08 (−0.31 to 0.16)	0.54	−0.04 (−0.16 to 0.08)	0.527

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

TABLE 49 Scale for the Assessment of Negative Symptoms outcomes at 15 months

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Unchanging facial expression	0.9 (1.2), 27	0.6 (1.0), 38	0.26 (−0.03 to 0.56)	0.080	0.13 (−0.01 to 0.28)	0.062
Decreased spontaneous movement	0.4 (0.8), 26	0.2 (0.6), 38	0.16 (−0.02 to 0.33)	0.076	0.10 (0.00 to 0.19)	0.044
Paucity of expressive gestures	0.8 (1.4), 26	0.4 (0.9), 38	0.22 (−0.05 to 0.49)	0.12	0.09 (−0.03 to 0.21)	0.16
Poor eye contact	0.9 (1.3), 27	0.7 (1.0), 38	0.16 (−0.11 to 0.43)	0.24	0.06 (−0.07 to 0.18)	0.39
Affective non-responsivity	0.5 (1.0), 26	0.3 (0.6), 38	0.18 (−0.03 to 0.40)	0.094	0.08 (−0.02 to 0.19)	0.12
Lack of vocal inflections	0.8 (1.2), 26	0.3 (0.7), 36	0.38 (0.13 to 0.63)	0.003	0.19 (0.07 to 0.31)	0.002
Global rating of affective flat	0.9 (1.1), 28	0.6 (0.8), 38	0.16 (−0.07 to 0.39)	0.18	0.08 (−0.04 to 0.20)	0.22
Inappropriate affect	0.2 (0.4), 26	0.2 (0.5), 38	0.01 (−0.11 to 0.13)	0.88	0.02 (−0.06 to 0.10)	0.62
Poverty of speech	0.7 (1.3), 22	0.5 (1.0), 36	0.20 (−0.05 to 0.45)	0.12	0.09 (−0.03 to 0.20)	0.15
Poverty of content of speech	0.5 (1.0), 22	0.3 (0.7), 36	0.16 (−0.06 to 0.39)	0.15	0.06 (−0.05 to 0.18)	0.27
Blocking	0.2 (0.6), 22	0.2 (0.6), 36	−0.02 (−0.18 to 0.15)	0.85	0.00 (−0.09 to 0.09)	1.00
Increased latency of response	0.5 (0.9), 23	0.2 (0.6), 36	0.23 (0.02 to 0.44)	0.028	0.12 (0.02 to 0.23)	0.024
Global rating of alogia	0.7 (0.8), 22	0.5 (0.7), 36	0.17 (−0.02 to 0.37)	0.087	0.10 (−0.01 to 0.21)	0.070

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

TABLE 50 Scale for the Assessment of Negative Symptoms outcomes at 15 months further data

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Grooming and hygiene	0.7 (1.1), 24	0.6 (1.0), 35	0.02 (−0.24 to 0.28)	0.86	0.00 (−0.13 to 0.13)	0.98
Impersistence at work or school	2.9 (2.0), 23	2.8 (2.1), 35	0.05 (−0.43 to 0.53)	0.85		
Physical anergia	2.0 (1.6), 23	2.0 (1.7), 35	0.02 (−0.38 to 0.43)	0.905		
Global rating of avolition apathy	2.3 (1.4), 24	2.2 (1.5), 36	0.13 (−0.23 to 0.48)	0.48		

TABLE 50 Scale for the Assessment of Negative Symptoms outcomes at 15 months further data (*continued*)

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Recreational interest and activity	1.4 (1.6), 24	1.4 (1.6), 35	−0.02 (−0.44 to 0.39)	0.91		
Sexual interest and activity	1.2 (1.8), 25	1.1 (1.7), 36	0.10 (−0.35 to 0.55)	0.65	0.04 (−0.14 to 0.22)	0.68
Ability to feel intimacy and closeness	1.0 (1.3), 24	1.0 (1.2), 35	0.02 (−0.30 to 0.34)	0.89	0.00 (−0.15 to 0.15)	0.99
Relationships with friends and peers	2.0 (1.7), 24	1.5 (1.7), 35	0.46 (0.03 to 0.89)	0.036		
Global rating of anhedonia asociality	1.8 (1.4), 25	1.6 (1.3), 35	0.17 (−0.18 to 0.51)	0.34		
Social inattentiveness	0.4 (0.8), 25	0.3 (0.9), 36	0.10 (−0.13 to 0.33)	0.40	0.07 (−0.05 to 0.18)	0.25
Inattentiveness during mental state testing	0.7 (1.1), 24	0.8 (1.3), 36	−0.09 (−0.37 to 0.19)	0.54	−0.03 (−0.16 to 0.10)	0.66
Global rating of attention	0.6 (0.8), 25	0.6 (0.9), 37	0.04 (−0.18 to 0.26)	0.73	0.03 (−0.08 to 0.15)	0.58

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

TABLE 51 Scale for the Assessment of Negative Symptoms outcomes at 24 months

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Unchanging facial expression	1.0 (1.3), 39	0.6 (1.1), 51	0.36 (0.02 to 0.70)	0.041	0.18 (0.03 to 0.34)	0.022
Decreased spontaneous movement	0.6 (1.1), 39	0.3 (0.8), 51	0.28 (−0.00 to 0.56)	0.051	0.15 (0.01 to 0.28)	0.033
Paucity of expressive gestures	1.1 (1.6), 39	0.5 (1.0), 51	0.52 (0.16 to 0.88)	0.005	0.22 (0.06 to 0.38)	0.007
Poor eye contact	1.0 (1.2), 39	0.6 (1.0), 51	0.34 (0.05 to 0.62)	0.023	0.17 (0.03 to 0.31)	0.014
Affective non-responsivity	0.6 (1.0), 39	0.3 (0.7), 51	0.27 (0.01 to 0.53)	0.042	0.15 (0.02 to 0.27)	0.025
Lack of vocal inflections	1.0 (1.3), 39	0.5 (1.0), 51	0.40 (0.08 to 0.73)	0.014	0.23 (0.08 to 0.37)	0.003
Global rating of affective flat	1.3 (1.2), 39	0.6 (1.0), 51	0.54 (0.25 to 0.82)	< 0.001	0.28 (0.15 to 0.41)	< 0.001
Inappropriate affect	0.1 (0.5), 38	0.2 (0.7), 51	−0.09 (−0.25 to 0.07)	0.26	−0.04 (−0.12 to 0.04)	0.35
Poverty of speech	0.7 (1.3), 39	0.4 (1.0), 50	0.27 (−0.01 to 0.55)	0.060	0.13 (−0.00 to 0.26)	0.052

continued

TABLE 51 Scale for the Assessment of Negative Symptoms outcomes at 24 months (*continued*)

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Poverty of content of speech	0.4 (0.8), 38	0.3 (0.8), 50	0.03 (−0.19 to 0.26)	0.76	0.02 (−0.10 to 0.13)	0.75
Blocking	0.4 (0.8), 39	0.3 (0.8), 51	0.11 (−0.10 to 0.32)	0.30	0.06 (−0.04 to 0.17)	0.23
Increased latency of response	0.5 (0.9), 39	0.4 (0.7), 50	0.04 (−0.20 to 0.28)	0.75	0.01 (−0.12 to 0.13)	0.89
Global rating of alogia	0.8 (1.0), 39	0.5 (0.8), 50	0.23 (−0.01 to 0.47)	0.057	0.12 (−0.01 to 0.25)	0.066

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

TABLE 52 Scale for the Assessment of Negative Symptoms outcomes at 24 months further data

Symptom	Allocation arm, mean (SD), *n* missing		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Grooming and hygiene	0.6 (1.1), 40	0.7 (1.2), 51	−0.15 (−0.45 to 0.15)	0.33	−0.08 (−0.22 to 0.07)	0.29
Impersistence at work or school	2.8 (2.1), 40	2.6 (2.1), 51	0.09 (−0.46 to 0.65)	0.74		
Physical anergia	2.2 (1.7), 40	2.2 (1.8), 51	−0.02 (−0.50 to 0.45)	0.92		
Global rating of avolition apathy	2.3 (1.6), 40	2.2 (1.6), 51	0.16 (−0.26 to 0.57)	0.45		
Recreational interest and activity	1.4 (1.6), 40	1.3 (1.4), 51	0.16 (−0.28 to 0.60)	0.48	0.02 (−0.17 to 0.21)	0.82
Sexual interest and activity	1.3 (1.8), 45	1.3 (1.8), 51	0.07 (−0.45 to 0.59)	0.78	0.02 (−0.19 to 0.22)	0.87
Ability to feel intimacy and closeness	1.0 (1.3), 40	1.0 (1.3), 51	0.03 (−0.33 to 0.38)	0.89	0.00 (−0.16 to 0.16)	0.97
Relationships with friends and peers	2.3 (1.9), 40	1.5 (1.5), 51	0.78 (0.31 to 1.26)	0.001		
Global rating of anhedonia asociality	2.0 (1.5), 40	1.6 (1.3), 51	0.43 (0.03 to 0.82)	0.034		
Social inattentiveness	0.3 (0.8), 41	0.3 (0.8), 51	−0.03 (−0.25 to 0.20)	0.81	−0.01 (−0.12 to 0.10)	0.84
Inattentiveness during mental state testing	0.9 (1.3), 42	0.8 (1.4), 51	0.08 (−0.28 to 0.44)	0.66	0.06 (−0.09 to 0.22)	0.42
Global rating of attention	0.7 (1.0), 42	0.6 (0.9), 51	0.07 (−0.19 to 0.33)	0.59	0.04 (−0.08 to 0.17)	0.509

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Per-protocol analysis of primary outcome

For the time use variables, we explored the analysis of the PP population as well as the ITT population. These results are presented in *Table 53*.

Time use linear models exploring interactions

When adding interaction terms (treatment arm × severity of social disability, or treatment arm × mental state risk) in turn to the linear models for the primary outcome measure (structured hours at 15 months), there is no evidence to suggest a difference between ESC-alone and ESC plus SRT arms, using either interaction term.

For the remainder of the time use outcome measures, when adding the interaction term (treatment arm × ARMS status), there is no evidence to suggest a difference between ESC alone and ESC plus SRT, for any of the time use variables. When adding the interaction term treatment arm × severity of social disability, *Table 54* shows the relevant results ($p < 0.1$).

For the ITT population, there is moderate evidence at 24 months of a difference in structured activity hours and constructive activity hours ($p = 0.032$ and $p = 0.048$, respectively), both in favour of the ESC-alone arm. It is estimated that, at 24 months, hours of average structured acitivity is 36.3% higher in the ESC-alone arm than in the ESC plus SRT group, and hours of constructive activity is 37.7% higher in the ESC-alone group. These are slightly larger differences in averages than if not including this interaction term within the linear model.

TABLE 53 Primary time use outcomes: analysis of PP population at 9 and 15 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
9 months						
Structured activity (hours per week)	19.4 (14.5)	22.3 (19.3)	−1.23 (−5.71 to 3.25)	0.59	0.09 (−0.14 to 0.32)	0.45
Missing, *n*	4	17				
Structured activity (minus child care; hours per week)	18.5 (12.8)	22.2 (19.3)	−2.04 (−6.41 to 2.34)	0.36	0.08 (−0.16 to 0.31)	0.52
Missing, *n*	4	17				
15 months						
Structured activity (hours per week)	18.0 (15.3)	27.7 (26.5)	−7.00 (−13.22 to −0.78)	0.028	−0.16 (−0.41 to 0.08)	0.19
Missing, *n*	4	24				
Structured activity (minus child care; hours per week)	17.6 (14.7)	24.9 (20.4)	−4.99 (−9.89 to −0.08)	0.046	−0.13 (−0.37 to 0.12)	0.31
Missing, *n*	4	24				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 54 Time use linear models for severity of social disability interactions

Population	Time point (months)	Outcome measure	Log-transformed	
			Adjusted difference (95% CI)	*p*-value
ITT	24	Structured activity hours per week	−0.31 (−0.60 to −0.03)	0.032
ITT	24	Constructive economic activity hours per week	−0.32 (−0.64 to −0.00)	0.048
PP	24	Structured activity hours per week	−0.37 (−0.69 to −0.06)	0.021
PP	24	Constructive economic activity hours per week	−0.35 (−0.70 to 0.00)	0.051
PP	24	Structured activity hours per week (minus child care)	−0.29 (−0.60 to 0.02)	0.070

Notes
General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect, and interaction term (treatment group × severity of social disability). 95% CIs for parameter estimates. The *p*-value is based on a null hypothesis of zero difference.

For the PP population, there is moderate ($p = 0.021$) and weak ($p = 0.051$) evidence of a difference in structured and constructive activity hours, respectively, at 24 months in favour of the ESC-alone arm. It is estimated that, at 24 months, hours of structured activity is, on average, 44.8% higher in the ESC-alone group than in the ESC plus SRT group, and hours of constructive activity is, on average, 41.9% higher in the ESC-alone group. As with the ITT population, these average differences are slightly higher than if not including this interaction term within the model. There is also weak evidence ($p = 0.070$) of a difference between treatment groups of structured activity hours not including child care at 24 months, favouring the ESC-alone arm, with an average of 33.6% more hours. This outcome measure was not found to be significant when not using an interaction term within the model. It is to be noted that the CIs for these adjusted differences (for ITT and PP) include or are very close to zero, which may affect the significance of these results.

Analysis of missing data for primary outcome

TABLE 55 Time use outcomes: analysis of missing data (FIML approach) at 9 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	21.4 (16.6)	22.3 (19.3)	0.89 (−3.09 to 4.88)	0.66	−0.07 (−0.27 to 0.13)	0.50
Missing, *n*	12	17				
Constructive economic activity (hours per week)	15.7 (14.3)	16.6 (15.9)	1.13 (−2.35 to 4.60)	0.53	0.01 (−0.22 to 0.23)	0.94
Missing, *n*	12	17				
Structured activity (minus child care; hours per week)	20.3 (14.7)	22.2 (19.3)	1.69 (−2.15 to 5.53)	0.39	−0.06 (−0.26 to 0.14)	0.56
Missing, *n*	12	17				
Total hours paid employment[d]	156.9 (432.3)	283.9 (511.4)	104.22 (−22.94 to 231.37)	0.108	0.64 (−0.13 to 1.40)	0.103
Missing, *n*	25	48				
Total hours education[d]	130.1 (353.3)	108.0 (235.0)	−23.32 (−110.22 to 63.59)	0.60	−0.17 (−0.88 to 0.53)	0.63
Missing, *n*	26	50				

TABLE 55 Time use outcomes: analysis of missing data (FIML approach) at 9 months (*continued*)

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Total hours voluntary employment[d]	50.5 (215.4)	50.7 (170.9)	3.95 (−50.52 to 58.41)	0.89	0.11 (−0.46 to 0.68)	0.702
Missing, *n*	33	47				
Total hours all activity[d]	349.1 (591.2)	454.2 (592.9)	87.39 (−76.36 to 251.14)	0.30	0.42 (−0.34 to 1.18)	0.28
Missing, *n*	35	56				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 56 Primary time use outcomes: analysis of missing data (FIML approach) at 15 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	22.4 (21.4)	27.7 (26.5)	4.38 (−1.18 to 9.94)	0.12	0.12 (−0.10 to 0.33)	0.28
Missing, *n*	11	24				
Constructive economic activity (hours per week)	17.4 (19.9)	22.0 (24.5)	4.36 (−0.90 to 9.62)	0.104	0.21 (−0.03 to 0.45)	0.080
Missing, *n*	11	24				
Structured activity (minus child care; hours per week)	21.1 (18.1)	24.9 (20.4)	2.94 (−1.42 to 7.30)	0.19	0.08 (−0.13 to 0.29)	0.45
Missing, *n*	11	24				
Total hours paid employment[d]	75.3 (213.8)	123.6 (275.2)	46.38 (−15.98 to 108.73)	0.15	0.30 (−0.30 to 0.89)	0.33
Missing, *n*	21	31				
Total hours education[d]	76.6 (174.1)	88.8 (176.3)	12.20 (−33.39 to 57.79)	0.60	0.26 (−0.36 to 0.87)	0.42
Missing, *n*	25	31				
Total hours voluntary employment[d]	16.5 (46.8)	36.8 (96.3)	19.05 (−0.47 to 38.57)	0.056	0.25 (−0.23 to 0.73)	0.308
Missing, *n*	27	28				

continued

TABLE 56 Primary time use outcomes: analysis of missing data (FIML approach) at 15 months (*continued*)

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Total hours all activity[d]	158.8 (252.0)	258.8 (359.8)	92.20 (172.34 to −12.05)	0.024	0.46 (−0.19 to 1.11)	0.17
Missing, *n*	34	35				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 57 Time use outcomes: analysis of missing data (FIML approach) at 24 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	24.3 (18.9)	32.4 (28.7)	7.40 (1.25 to 13.56)	0.018	0.20 (−0.03 to 0.43)	0.092
Missing, *n*	25	40				
Constructive economic activity (hours per week)	18.6 (16.7)	27.4 (28.0)	8.22 (2.38 to 14.06)	0.006	0.28 (0.02 to 0.54)	0.034
Missing, *n*	25	40				
Structured activity minus child care (hours per week)	23.8 (18.9)	26.6 (20.4)	2.34 (−2.68 to 7.35)	0.36	0.08 (−0.15 to 0.32)	0.48
Missing, *n*	25	40				
Total hours paid employment[d]	79.1 (218.8)	121.7 (277.7)	41.04 (−23.95 to 106.04)	0.22	0.25 (−0.37 to 0.86)	0.43
Missing, *n*	27	37				
Total hours education[d]	76.7 (175.3)	93.6 (182.4)	16.72 (−31.33 to 64.77)	0.50	0.27 (−0.37 to 0.91)	0.42
Missing, *n*	32	39				
Total hours voluntary employment[d]	14.3 (37.7)	38.3 (99.7)	23.89 (3.89 to 43.88)	0.019	0.31 (−0.18 to 0.80)	0.27
Missing, *n*	34	36				
Total hours all activity[d]	161.0 (255.0)	258.9 (364.5)	92.09 (8.90 to 175.28)	0.030	0.45 (−0.22 to 1.12)	0.19
Missing, *n*	39	40				

a General linear model used, adjusted for differences of the outcome variable at baseline, along with stratification variables, and neurocognitive performance (Logical Memory Immediate Recall total and COWAT total for the letters F, A, S), along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 58 Time use outcomes: analysis of missing data (MI approach) at 9 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	p-value[c]	Adjusted difference[a] (95% CI[b])	p-value[c]
Structured activity (hours per week)	21.4 (16.6)	22.3 (19.3)	−1.05 (−5.14 to 3.04)	0.61	0.08 (−0.12 to 0.28)	0.45
Missing, *n*	12	17				
Constructive economic activity (hours per week)	15.7 (14.3)	16.6 (15.9)	−1.13 (−4.71 to 2.45)	0.54	−0.02 (−0.25 to 0.22)	0.90
Missing, *n*	12	17				
Structured activity (minus child care; hours per week)	20.3 (14.7)	22.2 (19.3)	−1.68 (−5.58 to 2.22)	0.40	0.03 (−0.20 to 0.27)	0.78
Missing, *n*	12	17				
Total hours paid employment[d]	156.9 (432.3)	283.9 (511.4)	−112.32 (−240.74 to 16.11)	0.086	−0.63 (−1.40 to 0.13)	0.10
Missing, *n*	25	48				
Total hours education[d]	130.1 (353.3)	108.0 (235.0)	17.75 (−77.29 to 112.78)	0.71	0.13 (−0.60 to 0.87)	0.72
Missing, *n*	26	50				
Total hours voluntary employment[d]	50.5 (215.4)	50.7 (170.9)	−7.00 (−65.89 to 51.88)	0.82	−0.17 (−0.77 to 0.42)	0.57
Missing, *n*	33	47				
Total hours all activity[d]	349.1 (591.2)	454.2 (592.9)	−102.59 (−274.95 to 69.77)	0.24	−0.45 (−1.26 to 0.36)	0.28
Missing, *n*	35	56				

a The MI approach imputes the missing data $m = 50$ times, analyses each data set using a general linear model, then pools $m = 50$ results to yield a single estimate. General linear model used, adjusted for differences of the outcome variable at baseline, stratification variables, covariates logical memory and verbal fluency, along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 59 Time use outcomes: analysis of missing data (MI approach) at 15 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	p-value[c]	Adjusted difference[a] (95% CI[b])	p-value[c]
Structured activity (hours per week)	22.4 (21.4)	27.7 (26.5)	−4.45 (−10.05 to 1.14)	0.12	−0.13 (−0.35 to 0.09)	0.24
Missing, *n*	11	24				
Constructive activity (hours per week)	17.4 (19.9)	22.0 (24.5)	−4.68 (−10.10 to 0.74)	0.091	−0.23 (−0.47 to 0.01)	0.06
Missing, *n*	11	24				

continued

TABLE 59 Time use outcomes: analysis of missing data (MI approach) at 15 months (*continued*)

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (minus child care; hours per week)	21.1 (18.1)	24.9 (20.4)	−3.26 (−7.73 to 1.20)	0.15	−0.09 (−0.31 to 0.12)	0.41
Missing, *n*	11	24				
Total hours paid employment[d]	75.3 (213.8)	123.6 (275.2)	−45.73 (−108.62 to 17.16)	0.15	−0.31 (−0.94 to 0.32)	0.33
Missing, *n*	21	31				
Total hours education[d]	76.6 (174.1)	88.8 (176.3)	−9.13 (−55.47 to 37.22)	0.70	−0.27 (−0.91 to 0.37)	0.41
Missing, *n*	25	31				
Total hours voluntary employment[d]	16.5 (46.8)	36.8 (96.3)	−20.53 (−40.54 to −0.53)	0.044	−0.24 (−0.73 to 0.25)	0.34
Missing, *n*	27	28				
Total hours all activity[d]	158.8 (252.0)	258.8 (359.8)	−98.43 (−182.08 to −14.79)	0.021	−0.46 (−1.18 to 0.26)	0.21
Missing, *n*	34	35				

a The MI approach imputes the missing data $m = 50$ times, analyses each data set using a general linear model, then pools $m = 50$ results to yield a single estimate. General linear model used, adjusted for differences of the outcome variable at baseline, stratification variables, covariates logical memory and verbal fluency, along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

TABLE 60 Time use outcomes: analysis of missing data (MI approach) at 24 months

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC (*N* = 138)	ESC alone (*N* = 132)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (hours per week)	24.3 (18.9)	32.4 (28.7)	−7.54 (−13.83 to −1.25)	0.019	−0.21 (−0.46 to 0.04)	0.101
Missing, *n*	25	40				
Constructive activity (hours per week)	18.6 (16.7)	27.4 (28.0)	−8.40 (−14.44 to −2.37)	0.006	−0.29 (−0.56 to −0.02)	0.038
Missing, *n*	25	40				

TABLE 60 Time use outcomes: analysis of missing data (MI approach) at 24 months (*continued*)

Time use outcome	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Structured activity (minus child care; hours per week)	23.8 (18.9)	26.6 (20.4)	−2.52 (−7.85 to 2.80)	0.35	−0.08 (−0.33 to 0.17)	0.53
Missing, *n*	25	40				
Total hours paid employment[d]	79.1 (218.8)	121.7 (277.7)	−44.60 (−116.95 to 27.75)	0.23	−0.25 (−0.89 to 0.38)	0.44
Missing, *n*	27	37				
Total hours education[d]	76.7 (175.3)	93.6 (182.4)	−17.86 (−67.12 to 31.40)	0.48	−0.26 (−0.92 to 0.40)	0.44
Missing, *n*	32	39				
Total hours voluntary employment[d]	14.3 (37.7)	38.3 (99.7)	−24.08 (−44.50 to −3.66)	0.021	−0.30 (−0.86 to 0.26)	0.29
Missing, *n*	34	36				
Total hours all activity[d]	161.0 (255.0)	258.9 (364.5)	−100.51 (−188.96 to −12.07)	0.026	−0.46 (−1.18 to 0.27)	0.22
Missing, *n*	39	40				

a The MI approach imputes the missing data $m = 50$ times, analyses each data set using a general linear model, then pools $m = 50$ results to yield a single estimate. General linear model used, adjusted for differences of the outcome variable at baseline, stratification variables, covariates logical memory and verbal fluency, along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d No baseline information available, so baseline model adjustment was not made for this outcome variable.

Note
Structured activity of < 30 hours per week reflects low functioning, with < 15 hours per week reflecting very low functioning.

Analysis of missing data: comparison of methods

The proportion of CAARMS data missing at 24 months was high. For example, CAARMS average distress was missing for 64.4% of those in the ESC-alone arm and for 60.0% of those in the SRT plus ESC arm; similarly, aggression severity score was missing for 62.9% of participants in the ESC-alone arm and for 55.8% of those in the SRT plus ESC arm.

Owing to this high proportion of missing data, a missing data analysis was undertaken for these outcome measures using two different analysis methods: MI and FIML. The results are very similar to the outcomes presented in *Table 55*, with the CAARMS average distress score at 24 months having moderate evidence ($p = 0.020$) of a difference. On average, the SRT plus ESC arm scored 11.36 higher than the ESC-alone arm. There was also weak evidence of a difference in the CAARMS aggression severity score at 24 months ($p = 0.059$), with the SRT plus ESC arm scoring, on average, 1.80 higher than the ESC-alone arm. A comparison of methods is presented in *Table 62* and shows no evidence of a difference between missing data analysis approaches.

TABLE 61 CAARMS severity secondary outcomes at 24 months

CAARMS score	Allocation arm, mean (SD)		Untransformed		Log-transformed	
	SRT + ESC ($N = 138$)	ESC alone ($N = 132$)	Adjusted difference[a] (95% CI[b])	*p*-value[c]	Adjusted difference[a] (95% CI[b])	*p*-value[c]
Symptom severity score	20.4 (21.3)	20.2 (19.4)	1.45 (−5.54 to 8.44)	0.68		
Missing, *n*	79	86				
Average distress score	42.8 (26.6)	31.0 (26.5)	11.64 (1.29 to 22.00)	0.028		
Missing, *n*	80	85				
Aggression severity score	5.0 (5.5)	3.5 (5.2)	1.86 (−0.16 to 3.88)	0.071		
Missing, *n*	77	83				
Suicidality severity score	4.3 (6.6)	3.8 (5.9)	0.74 (−1.46 to 2.95)	0.505	0.11 (−0.29 to 0.52)	0.58
Missing, *n*	77	82				

a General linear model used, adjusted for differences of the outcome variable at baseline, stratification variables, covariates logical memory and verbal fluency, along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.

Notes
CAARMS symptom severity reflects the product of global severity (scored 0–6) and frequency (scored 0–6) for four positive symptom subscales. CAARMS distress reflects the average distress score (scored 0–100) for four positive symptom subscales. CAARMS aggression and suicidality severity scores reflect the respective products of global severity (scored 0–6) and frequency scores (scored 0–6). Higher scores reflect more severe symptoms.

TABLE 62 CAARMS severity secondary outcomes at 24 months (variables with high proportions of missing data): comparison of missing data analysis methods

Missing data method	CAARMS severity secondary outcome measure (at 24 months)	Adjusted difference[a] (95% CI[b])	*p*-value[c]
FIML	Average distress score	11.36[d] (1.77 to 20.96)	0.020
MI	Average distress score	11.83[e] (1.50 to 22.16)	0.025
FIML	Aggression severity score	1.80[d] (−0.07 to 3.67)	0.059
MI	Aggression severity score	1.66[e] (−0.26 to 3.59)	0.090

a General linear model used, adjusted for differences of the outcome variable at baseline, stratification variables, covariates logical memory and verbal fluency, along with study site as a random effect.
b 95% CIs for parameter estimates.
c The *p*-value is based on a null hypothesis of zero difference.
d For FIML method, this estimates parameter values directly from the incomplete data set (without having to impute/delete missing/incomplete values), using all available information to maximise the likelihood function of the incomplete data.
e For MI method, this imputes the missing data $m = 50$ times, analyses each data set using a general linear model, then pools $m = 50$ results to yield a single estimate.

Appendix 4 Adverse event definitions

TABLE 63 Adverse event definitions

Event	Definition
AE	Any untoward medical occurrence in a patient or clinical trial participant that does not necessarily have a causal relationship with this product AEs include an exacerbation of a pre-existing illness, an increase in the frequency or intensity of a pre-existing episodic event or condition, a condition (regardless of whether or not present prior to the start of the trial) that is detected after trial intervention administration (this does not include pre-existing conditions recorded as such at baseline), and continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment AEs do not include medical or surgical procedures, pre-existing disease or a condition present before treatment that does not worsen, hospitalisation where no untoward or unintended response has occurred (e.g. elective cosmetic surgery), and overdose of medication without signs or symptoms
Adverse reaction	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected adverse reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised product or summary of product characteristics for an authorised product)
SAE or serious adverse reaction	Any AE or adverse reaction that at any dose: • results in death • is life-threatening[a] • requires hospitalisation or prolongs existing hospitalisation[b] • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • is another important medical condition[c]

a The term life-threatening refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction).
b Hospitalisation is defined as an inpatient admission of any length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute a SAE.
c Medical judgement should be exercised in deciding whether an AE or adverse reaction is serious in other situations. Important AEs or adverse reactions may not be immediately life-threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

EME
HS&DR
HTA
PGfAR
PHR

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