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Specialised early intervention teams for recent-onset psychosis (Review)

Puntis S, Minichino A, De Crescenzo F, Harrison R, Cipriani A, Lennox B

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[Intervention Review]

Specialised early intervention teams for recent-onset psychosis

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ABSTRACT

Background

Psychosis is an illness characterised by the presence of hallucinations and delusions that can cause distress or a marked change in an individual's behaviour (e.g. social withdrawal, flat or blunted affect). A first episode of psychosis (FEP) is the first time someone experiences these symptoms that can occur at any age, but the condition is most common in late adolescence and early adulthood. This review is concerned with first episode psychosis (FEP) and the early stages of a psychosis, referred to throughout this review as 'recent-onset psychosis.'

Specialised early intervention (SEI) teams are community mental health teams that specifically treat people who are experiencing, or have experienced a recent-onset psychosis. The purpose of SEI teams is to intensively treat people with psychosis early in the course of the illness with the goal of increasing the likelihood of recovery and reducing the need for longer-term mental health treatment. SEI teams provide a range of treatments including medication, psychotherapy, psychoeducation, and occupational, educational and employment support, augmented by assertive contact with the service user and small caseloads. Treatment is time limited, usually offered for two to three years, after which service users are either discharged to primary care or transferred to a standard adult community mental health team. A previous Cochrane Review of SEI found preliminary evidence that SEI may be superior to standard community mental health care (described as 'treatment as usual (TAU)' in this review) but these recommendations were based on data from only one trial. This review updates the evidence for the use of SEI services.

Objectives

To compare specialised early intervention (SEI) teams to treatment as usual (TAU) for people with recent-onset psychosis.

Search methods

On 3 October 2018 and 22 October 2019, we searched Cochrane Schizophrenia's study-based register of trials, including registries of clinical trials.

Selection criteria

We selected all randomised controlled trials (RCTs) comparing SEI with TAU for people with recent-onset psychosis. We entered trials meeting these criteria and reporting useable data as included studies.

Data collection and analysis

We independently inspected citations, selected studies, extracted data and appraised study quality. For binary outcomes we calculated the risk ratios (RRs) and their 95% confidence intervals (CIs). For continuous outcomes we calculated the mean difference (MD) and their 95% CIs, or if assessment measures differed for the same construct, we calculated the standardised mean difference (SMD) with 95% CIs. We assessed risk of bias for included studies and created a 'Summary of findings' table using the GRADE approach.

Main results

We included three RCTs and one cluster-RCT with a total of 1145 participants. The mean age in the trials was between 23.1 years (RAISE) and 26.6 years (OPUS). The included participants were 405 females (35.4%) and 740 males (64.6%). All trials took place in community mental healthcare settings.

Two trials reported on recovery from psychosis at the end of treatment, with evidence that SEI team care may result in more participants in recovery than TAU at the end of treatment (73% versus 52%; RR 1.41, 95% CI 1.01 to 1.97; 2 studies, 194 participants; low-certainty evidence).

Three trials provided data on disengagement from services at the end of treatment, with fewer participants probably being disengaged from mental health services in SEI (8%) in comparison to TAU (15%) (RR 0.50, 95% CI 0.31 to 0.79; 3 studies, 630 participants; moderate-certainty evidence).

There was low-certainty evidence that SEI may result in fewer admissions to psychiatric hospital than TAU at the end of treatment (52% versus 57%; RR 0.91, 95% CI 0.82 to 1.00; 4 studies, 1145 participants) and low-certainty evidence that SEI may result in fewer psychiatric hospital days (MD -27.00 days, 95% CI -53.68 to -0.32; 1 study, 547 participants).

Two trials reported on general psychotic symptoms at the end of treatment, with no evidence of a difference between SEI and TAU, although this evidence is very uncertain (SMD -0.41, 95% CI -4.58 to 3.75; 2 studies, 304 participants; very low-certainty evidence). A different pattern was observed in assessment of general functioning with an end of trial difference that may favour SEI (SMD 0.37, 95% CI 0.07 to 0.66; 2 studies, 467 participants; low-certainty evidence).

It was uncertain whether the use of SEI resulted in fewer deaths due to all-cause mortality at end of treatment (RR 0.21, 95% CI 0.04 to 1.20; 3 studies, 741 participants; low-certainty evidence).

There was low risk of bias for random sequence generation and allocation concealment in three of the four included trials; the remaining trial had unclear risk of bias. Due to the nature of the intervention, we considered all trials at high risk of bias for blinding of participants and personnel. Two trials had low risk of bias and two trials had high risk of bias for blinding of outcomes assessments. Three trials had low risk of bias for incomplete outcome data, while one trial had high risk of bias. Two trials had low risk of bias, one trial had high risk of bias, and one had unclear risk of bias for selective reporting.

Authors' conclusions

There is evidence that SEI may provide benefits to service users during treatment compared to TAU. These benefits probably include fewer disengagements from mental health services (moderate-certainty evidence), and may include small reductions in psychiatric hospitalisation (low-certainty evidence), and a small increase in global functioning (low-certainty evidence) and increased service satisfaction (moderate-certainty evidence). The evidence regarding the effect of SEI over TAU after treatment has ended is uncertain. Further evidence investigating the longer-term outcomes of SEI is needed. Furthermore, all the eligible trials included in this review were conducted in high-income countries, and it is unclear whether these findings would translate to low- and middle-income countries, where both the intervention and the comparison conditions may be different.

PLAIN LANGUAGE SUMMARY

Is recent-onset psychosis best treated by a specialist mental health team?

What is psychosis?

Psychosis describes conditions affecting the mind, in which people have trouble distinguishing what is real from what is not real. This might involve seeing or hearing things that other people cannot see or hear (hallucinations), or believing things that are not true (delusions). The combination of hallucinations and delusional thinking can cause severe distress and a change in behaviour. A first episode psychosis is the first time a person experiences an episode of psychosis. Recent-onset psychosis is the first few years of the illness after someone experiences it for the first time.

Psychosis is treatable

Many people recover from a first episode and never experience another psychotic episode.

Mental health professionals assess a person before recommending a specific treatment. Depending on the services available, they may send people for treatment to:

- a community mental health team: mental health professionals who support people with complex mental health conditions;
- a crisis resolution team: mental health professionals who treat people who would otherwise need treatment in hospital; or
- an early intervention team: mental health professionals who work with people who are currently or have recently experienced their first episode of psychosis.

Early intervention teams specialise in treating recent-onset psychosis, and aim to treat it as quickly and intensively as possible.

Why we did this Cochrane Review

We wanted to find out whether specialist early intervention teams were more successful at treating recent-onset psychosis than outpatient or community mental health teams that do not specialise in treating it.

What did we do?

We searched for studies that investigated the use of early intervention teams to treat recent-onset psychosis compared with standard community mental health care.

We looked for randomised controlled studies, in which the treatments people received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment.

We wanted to find out, at the end of the treatment:

- how many people recovered;
- how many people stopped their treatment too soon;
- how many people were admitted to a psychiatric hospital, and for how long;
- the state of people's general mental health and functioning (how well they coped with daily life); and
- how many people died.

Search date: we included evidence published up to 22 October 2019.

What we found

We found four studies in 1145 people (65% men; average age 23 to 26 years) with recent-onset psychosis. The studies compared treatment by specialist early intervention teams against 'usual treatment' (treatment by community health or outpatient mental health teams).

The studies took place in community mental health services in high-income countries: Denmark, Sweden, the UK and the USA. The studies lasted from 18 to 24 months.

What are the results of our review?

Compared with usual treatment, treatment by an early intervention team:

- may help more people recover from psychosis (2 studies; 194 people);
- probably reduces how many people stop their treatment too soon (3 studies; 630 people);
- may reduce the number of people admitted to a psychiatric hospital (4 studies; 1145 people)
- may reduce the time spent in a psychiatric hospital (1 study; 547 people); and
- may moderately improve people's general functioning (2 studies; 467 people).

We were uncertain about whether treatment by an early intervention team affects general psychotic symptoms (2 studies; 304 people), or its effect on how many people died (3 studies; 741 people).

How reliable are these results?

We are moderately confident that treatment by an early intervention team probably reduces the number of people who stop treatment too soon, although this result may change when more evidence is available.

We are less confident about how many people recover from psychosis, or are admitted to a psychiatric hospital, how long they stay in hospital, and any improvements in people's general functioning. These results are likely to change when more evidence is available.

Key message

Using specialist early intervention teams to treat recent-onset psychosis is likely to have benefits, such as more people continuing with their treatment, and increasing the number of people who recover.

SUMMARY OF FINDINGS

Summary of findings 1. Specialised early intervention (SEI) compared to treatment as usual (TAU) for recent-onset psychosis at end of treatment

SEI compared to TAU for recent-onset psychosis at end of treatment

Patient or population: recent-onset psychosis (less than three years since the start of psychotic symptoms and either first or second psychotic episode)

Setting: community mental health

Intervention: specialised early intervention team care

Comparison: treatment as usual

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TAU	Risk with SEI				
Global state: recovery (assessed by proportion recovered, as defined by the study, at end of treatment)	Study population		RR 1.41 (1.01 to 1.97)	194 (2 RCTs)	⊕⊕⊕⊖ Low ^{a,b}	
	516 per 1000	728 per 1000 (521 to 1000)				
Service use: disengagement from services (assessed by proportion disengaged, as defined by the study, at end of treatment)	Study population		RR 0.50 (0.31 to 0.79)	630 (3 RCTs)	⊕⊕⊕⊖ Moderate ^b	
	150 per 1000	75 per 1000 (47 to 119)				
Service use: admission to psychiatric hospital (assessed by proportion admitted at end of treatment)	Study population		RR 0.91 (0.82 to 1.00)	1145 (4 RCTs)	⊕⊕⊕⊖ Low ^e	
	566 per 1000	515 per 1000 (464 to 566)				
Service use: number of days in psychiatric hospital (assessed by mean number of days in hospital at end of treatment)	The mean number of days in psychiatric hospital (end of treatment) in the TAU group was 123 days	MD 27 days fewer (53.68 fewer to 0.32 fewer)	-	547 (1 RCT)	⊕⊕⊕⊖ Low ^e	
Mental state: average endpoint score on a general mental state scale (general psychopathology,	-	SMD 0.41 points lower (4.58 lower to 3.75 higher)	-	304 (2 RCTs)	⊕⊕⊕⊖ Very low ^{c,d,e}	SMD of 0.50 represents a mod-

assessed by PANNS at end of treatment) ^g					erate ef- fect size (Cohen 1988)	
Death: all-cause mortality (assessed by proportion deceased at end of treatment)	Study population		RR 0.21 (0.04 to 1.20)	741 (3 RCTs)	⊕⊕⊕⊕ Low ^f	
	19 per 1000	4 per 1000 (1 to 23)				
Functioning: average endpoint score on general functioning scale (global functioning, assessed by questionnaire at end of treatment)	-	SMD 0.37 points higher (0.07 higher to 0.66 high- er)	-	467 (2 RCTs)	⊕⊕⊕⊕ Low ^{c,d}	SMD of 0.50 rep- resents a mod- erate ef- fect size (Cohen 1988)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **SMD:** standardised mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SEI:** specialised early intervention; **TAU:** treatment as usual

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded one level due to indirectness. Use of surrogate outcome. Outcome assessment differs between trials.

^bDowngraded one level due to imprecision. Wide confidence intervals.

^cDowngraded one level due to risk of bias. Non-blinded trials with subjective outcome, where outcomes assessor was either not blinded or allocation could easily be guessed by assessor.

^dDowngraded one level due to indirectness. Average scores from scales used to measure outcome instead of clinically important change.

^eDowngraded two levels due to imprecision. Few events, wide confidence intervals and small sample size.

^fDowngraded one level due to imprecision. Few events and wide confidence intervals.

^g Both studies used the PANNS scale to measure general psychopathology, but the **LEO** trial used an edited version with a smaller score range.

BACKGROUND

Description of the condition

The lifetime prevalence of psychotic illness is estimated to be 4 per 1000 of the population, with first episode psychosis (FEP) incidence estimated at 34 new cases per 100,000 person-years (Kirkbride 2012; Kirkbride 2017). Psychosis can occur at any age, but most people develop it in late adolescence and early adulthood, with a mean age of onset in the early twenties (Kirkbride 2017). Features of psychosis include hallucinations, delusions and disordered thinking (referred to as positive symptoms) and social withdrawal, flat or blunted affect, and poverty of speech (referred to as negative symptoms) (APA 2013). Psychotic illness encompasses a range of diagnoses, including schizophrenia and schizoaffective disorder, bipolar affective disorder and psychotic depression (WHO 2018). The impact on the individual is often significant; a psychotic illness has wide-ranging implications on quality of life and disability, including effects on physical health, social functioning, social inclusion, and education and employment (Mason 1995; Meltzer 2002).

There is no consensus on the definition of FEP (Breitborde 2009). There may be a considerable delay between the onset of a person's symptoms and their being referred to, and treated by, mental health services (Birchwood 2013). The pathways to care for people with psychosis can also often involve multiple failed attempts at obtaining treatment before mental health services are able to successfully start a treatment regime (Lincoln 1998). As a result, clinical services and research studies use proxy measures for FEP. These are most commonly a 'duration criteria' (e.g. less than three years since first onset of symptoms), a 'contact with mental health services' criteria (e.g. first contact with mental health services), or an initiation of antipsychotic medication criteria (e.g. no more than 6 months of antipsychotic prescriptions). In this review, we will refer to FEP and the early stages of a psychosis as 'recent-onset psychosis' in order to capture this uncertainty.

Schizophrenia and related psychotic illnesses are major contributors to the global burden of disease, with the associated annual economic costs estimated to range between USD 94 million and USD 102 billion by country (Chong 2016; Murray 1996). People with recent-onset psychosis can reach remission of psychotic symptoms and functional recovery following an episode of psychosis, but many relapse, and as the number of relapses increases, the likelihood of remission decreases (Morgan 2014; Wiersma 1998). Recent studies have challenged the historically orthodox view that the course of a psychotic illness is deteriorating and progressive. A meta-analysis on recovery after a first episode of psychosis estimated a 58% rate of remission and a 38% rate of recovery (Lally 2017). Long-term outcome studies have also shown high rates of symptomatic recovery and (to a lesser extent) functional and social recovery in people being treated for recent-onset psychosis (Revier 2015).

The growing optimism of remission and recovery following a psychotic episode has been complemented by services with a strong recovery-oriented purpose that aim to intensively and assertively treat those with early psychosis in order to improve and enhance this recovery (Singh 2017).

Description of the intervention

A specialised early intervention (SEI) service is a phase-specific multidisciplinary community mental health team that treats people experiencing, or who have recently experienced, their first episode of a psychotic illness (Fusar-Poli 2017). The objectives of SEI services are two-fold: first, they aim to intervene at an early stage of the illness, reducing the duration of untreated psychosis; second, they aim to provide a comprehensive package of treatment including medication, psychological therapies, and patient and family education, all backed by assertive case management (NICE 2014). The service model is of standalone, multidisciplinary community teams that provide an assertive outreach model of care, with care co-ordinators having a restricted caseload size to enable them to work intensively with patients and engage them in treatment (RCPsych 2016). The aim of SEI is to reduce impairment and facilitate recovery, and in turn, improve prognosis.

SEI services are time-limited to two or three years of treatment (depending on region and health service provision), with the rationale that early intensive treatment will preclude the need for such intensive treatment on an ongoing basis (i.e. a secondary prevention approach).

How the intervention might work

One of the most vocal arguments for the development of early phase treatments is that there is evidence of a 'critical period' in FEP (Birchwood 1998). This period, during the first few years of a psychotic illness, is potentially a period of rapid biological, psychological, and social changes, after which is followed by an eventual plateau of illness severity and functioning (Birchwood 1998). This trajectory of fluctuation of illness in the early years, followed by gradual deterioration has been found to be strongly predictive of later outcomes (Harrison 2001; Wiersma 1998). Standard community mental health teams had particular difficulty engaging this population, making it more challenging to deliver treatment (Birchwood 2014). SEI was developed primarily to improve engagement through assertive outreach, reducing the time to treatment (thereby reducing the duration of untreated psychosis) and potentially minimising the long-term burden of the illness (Fusar-Poli 2017). It is not clear however, whether SEI prevents poor outcomes, or alternatively, prevents poor outcomes only as long as SEI treatment is given.

Why it is important to do this review

SEI services are now considered the gold standard of care for people with recent-onset psychosis in the UK, USA, Europe, and Australasia. In the UK it is the recommended treatment by the National Institute for Health and Care Excellence (NICE 2014), and timely access to SEI was the first National Health Service (NHS) waiting time standard for mental health care (NHS England 2015). Despite their widespread use, a previous Cochrane Review of early interventions for psychosis only found one eligible randomised control trial (RCT) of specialist team interventions for recent-onset psychosis (Marshall 2011). A number of new RCTs comparing various forms of SEI to treatment as usual (TAU) have since been published (for example, GET UP PIANO 2013 and Kane 2016), and a recent meta-analysis of SEI in the treatment of 'early phase psychosis', which included trials that recruited participants with multiple acute psychotic episodes or people who had already had lengthy community treatment (e.g. up to five years), found SEI

superior to standard community mental health care in reducing treatment discontinuation, admission to psychiatric hospital, and psychotic symptoms (Correll 2018). It is important to do this review to ensure that new evidence for SEI services is evaluated.

OBJECTIVES

To compare specialised early intervention (SEI) teams to treatment as usual (TAU) for people with recent-onset psychosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) regardless of blinding, but excluded quasi-randomised studies, such as those that allocated interventions by alternate days of the week. Given the nature of the intervention, it would have been difficult to blind participants and clinicians from whether they were receiving the intervention or control condition and so we included both single- and double-blinded studies. Where people were given additional treatments as well as specialised early intervention (SEI) for recent-onset psychosis, we only included data if the adjunct treatment was evenly distributed between groups and it was only the SEI teams that were randomised. We did not exclude studies offering alternative models of care, such as step-down care, following discharge from the early intervention team.

Types of participants

SEI services are designed to treat people in the early stages of psychosis. Exact eligibility criteria for services often differ both within and between regions and countries, but generally have a 'time since onset' criterion and a 'number of onsets' criterion. We included participants who were within three years of the onset of their first psychotic episode (time since onset) with a first or second episode of psychosis (number of onsets). We included participants who were exhibiting symptoms that matched the criteria for primary psychotic diagnoses according to standardised criteria, such as the Diagnostic and Statistical Manual of Mental Disorders: DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000), DSM-5 (APA 2013), ICD-10 (WHO 2004), ICD-11 (WHO 2018) or Melbourne Criteria (Yung 2008). We excluded trials where participants had organic psychoses or head injury, and studies that recruited participants with prodromal symptoms (also known as 'at-risk mental states') who had not yet transitioned to a psychotic episode. We also excluded trials that included participants whose onset of illness is longer than three years, unless we could extract data on only the eligible participants.

Types of interventions

Specialised early intervention (SEI) team care

These are multidisciplinary, standalone, community-based mental health teams that take referrals for patients who have recent-onset psychosis. SEI teams are an alternative, rather than an addition, to standard psychiatric care.

In order to be defined as a SEI service, the intervention had to provide the following.

- Be multidisciplinary, standalone community-based mental health teams that take referrals for patients who have recent-onset psychosis and which is an alternative to, rather than an addition to, standard psychiatric care. Teams can share facilities with other health providers (for example, a community mental health team) but must operate independently from them. For example, having a separate caseload, separate team meetings, and a dedicated programme specifically aimed at the recent-onset psychosis caseload.
- Provide a package of treatment options that could include (but is not limited to) medication, psychological therapies, psychoeducation to the service user and carers, employment support, and physical health interventions (e.g. smoking cessation, physical health checks). These should be structured around regular, assertive outreach.
- Accept service users on to the caseload who are in the first or second episode of psychosis and are within three years of the onset of their psychosis.

Treatment as usual (TAU)

TAU for people with recent-onset psychosis differs by country, but usually consists of a community-based or outpatient mental health team that does not provide specialist, phase-specific (i.e. centred on the early phase of a psychotic illness) treatment.

Types of outcome measures

Timing of outcome assessment

We recorded post-treatment outcomes and any available outcomes reported at follow-up time points. Where appropriate, and if the data were available, we aimed to categorise treatment outcomes into end of treatment, medium-term follow-up (1 to 60 months post-intervention), and long-term follow-up (longer than 60 months post-intervention).

Primary outcomes

- Global state
 - * Recovery, as defined by the study
- Service use
 - * Disengagement from services, as defined by the study

Secondary outcomes

- Service use
 - * Admission to psychiatric hospital
 - * Readmission to psychiatric hospital
 - * Number of days in psychiatric hospital
- Global state
 - * Relapse, as defined by the study

- Mental state
 - * General
 - ☐ Clinically important change in general mental state
 - ☐ Any change in general mental state
 - ☐ Average endpoint/change score on a general mental state scale
 - * Specific
 - ☐ Clinically important change in positive symptoms (delusions, hallucinations, disordered thinking), as defined by individual studies
 - ☐ Any change in positive symptoms (delusions, hallucinations, disordered thinking), as defined by individual studies
 - ☐ Clinically important change in negative symptoms (avolition, poor self-care, blunted affect), as defined by individual studies
 - ☐ Any change in negative symptoms (avolition, poor self-care, blunted affect), as defined by individual studies
 - ☐ Clinically important change in depression, as defined by individual studies
 - ☐ Any change in depression, as defined by individual studies
 - ☐ Average endpoint/change score on specific symptoms mental state scale/subscale
- Behaviour
 - * Specific
 - * Occurrence of violent incidents (to self, others or property)
- Adverse effects/events
 - * General
 - ☐ At least one adverse effect/event
 - ☐ Average endpoint/change score on adverse effect scale
 - * Specific
 - ☐ Incidence of any specific adverse effects, as defined by individual studies
- Leaving the study early
 - * For any reason
 - * Due to adverse effect
- Quality of life (recipient or informal carers or professional carers)
 - * Overall
 - ☐ Clinically important change in overall quality of life
 - ☐ Average endpoint/change score on quality of life scale
- Functioning
 - * General
 - ☐ Clinically important change in general functioning
 - ☐ Average endpoint/change score on general functioning scale
 - * Specific (including social, cognitive, life skills)
 - ☐ Clinically important change in specific functioning
 - ☐ Average endpoint/change score on specific functioning scale
 - ☐ Any change in educational status
 - ☐ Any change in employment status

- Satisfaction with care (including subjective well-being and family burden)
 - * Recipient
 - ☐ Recipient satisfied with care
 - ☐ Average endpoint/change score on satisfaction scale
 - * Carers
 - ☐ Carer satisfied with care
 - ☐ Average endpoint/change score on satisfaction scale

'Summary of findings' table

We used the GRADE approach to interpret findings ([Schünemann 2011](#)); and used GRADEpro GDT to export data from Review Manager 5 (RevMan 5) to create a 'Summary of findings' table. A 'Summary of finding' table provides outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision making. We selected the following main outcomes for inclusion in the 'Summary of findings' table.

- Global state: recovery, as defined by each study (at end of treatment).
- Service use: disengagement from services, as defined by each study (at end of treatment).
- Service use: admission to psychiatric hospital (at end of treatment).
- Service use: number of days in psychiatric hospital (at end of treatment).
- Mental state: clinically important change in general mental state (at end of treatment).
- Adverse effects/events: death - all-cause mortality (at end of treatment).
- Functioning: specific - clinically important change in social functioning (at end of treatment).

If data were not available for these prespecified outcomes but were available for ones that are similar, we presented the closest outcome to the prespecified one in the table but took this into account when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia's study-based register of trials

On 3 October 2018, the Information Specialist searched the register using the search strategy described below. An update of this search strategy was conducted on 22 October 2019.

(*Early Intervention* AND *Special*) in Intervention Field of STUDY

In such study-based registers, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics ([Shokraneh 2017](#); [Shokraneh 2018](#)).

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their

monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings. There are no language, date, document type, or publication status limitations for inclusion of records into the register. For the full search strategies used to build Cochrane Schizophrenia's study-based register of trials, please see: schizophrenia.cochrane.org/register-trials.

Searching other resources

Reference searching

We inspected references of all included studies for further relevant studies.

Personal contact

We contacted known experts in the field for information regarding unpublished trials. We noted the outcome of this contact in the 'Characteristics of included studies' and 'Characteristics of ongoing studies' tables.

Data collection and analysis

Selection of studies

Review authors SP and AM independently inspected citations from the searches and identified relevant abstracts; FDC independently re-inspected a random 20% sample of the abstracts to ensure reliability of selection. Where disputes arose, we acquired the full report for more detailed scrutiny. SP and AM obtained and inspected full reports of the abstracts or reports meeting the review criteria. FDC re-inspected a random 20% of these full reports in order to ensure reliability of selection. In case of disagreement, we involved another member of the review team (BL) to reach a final decision. We resolved all disagreements by discussion, and therefore did not need to attempt to contact the authors of the study concerned for clarification.

Data extraction and management

Extraction

Review authors SP, AM, and RH independently extracted data from all included studies. We attempted to extract data presented only in graphs and figures whenever possible, but included the data only if two review authors independently obtained the same result. SP and AM discussed any disagreement and documented our decisions. If necessary, we attempted to contact authors through an open-ended request in order to obtain missing information, or for clarification. AC and BL helped clarify issues regarding any remaining problems and we documented these final decisions.

Management

Forms

We extracted data onto standard, predesigned, simple forms.

Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
- the measuring instrument had not been written or modified by one of the trialists for that particular trial; and

- the instrument should have been a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable.

However there were exceptions; we included subscores from mental state scales measuring positive and negative symptoms of schizophrenia where subscales had been previously validated in the empirical literature and were commonly used. Ideally, the measuring instrument should have either been i) a self-report; or ii) completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we noted if this was the case or not.

Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only used change data if the former were not available (Deeks 2011).

Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant continuous data before inclusion.

Endpoint data from studies with fewer than 200 participants

When a scale started from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than one, it strongly suggested that the data are skewed and we excluded these data. If this ratio was higher than one but less than two, there was a suggestion that the data are skewed: we entered these data and tested whether their inclusion or exclusion would change the results substantially. If such data changed the results we entered them as 'other data'. Finally, if the ratio was larger than two we included these data, because it is less likely that they are skewed (Altman 1996).

If a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986), we modified the calculation described above to take the scale starting point into account. In these cases skewed data are present if $2\text{ SD} > (S - S_{\min})$, where S is the mean score and ' S_{\min} ' is the minimum score.

Please note: we entered all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We also entered all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

Common measurement

To facilitate comparison between trials we aimed, where relevant, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicates a favourable outcome for SEI. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved') we reported data where the left of the line indicated an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

All included studies had two independent 'Risk of bias' assessments. Review authors SP, AM, and RH worked

independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a).

If the raters disagreed, we made the final rating by consensus. We reported non-concurrence in quality assessment, but if disputes arose regarding the category to which a trial is to be allocated, we resolved this by discussion.

We note the level of risk of bias in both the text of the review, Figure 1 and Figure 2, and the 'Risk of bias' tables.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

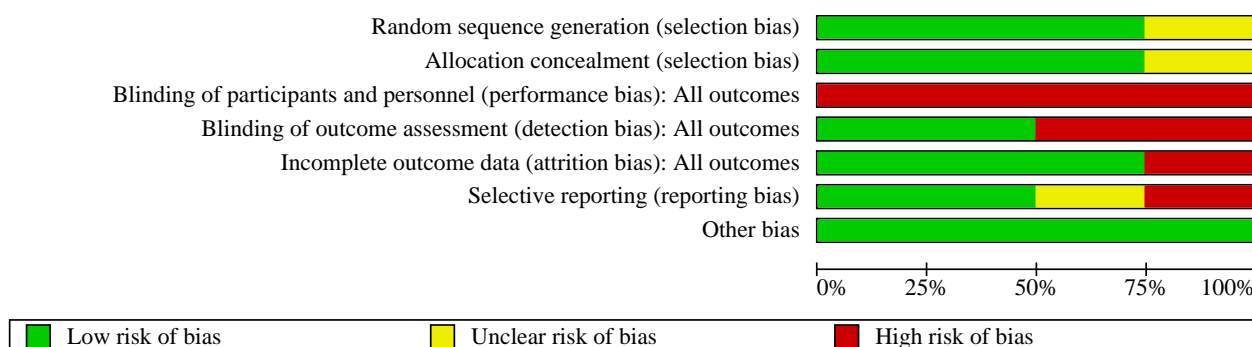


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
LEO							
OPUS							
OTP							
RAISE							

Measures of treatment effect

Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). For binary

data presented we calculated illustrative comparative risks ([Hutton 2009](#)).

Continuous data

For continuous outcomes we attempted to estimate the mean difference (MD) between groups if the measurement scales were the same, otherwise we used standardised mean difference (SMD).

Unit of analysis issues

Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intraclass correlation in clustered studies, leading to a unit of analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering had been incorporated into the analysis of primary studies, we presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

Where clustering had not been accounted for in primary studies, we presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We sought to contact first authors of studies to obtain intraclass correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation

coefficient (ICC): thus design effect = $1 + (m - 1) * ICC$ (Donner 2002). If the ICC was not reported we assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed and taken intraclass correlation coefficients and relevant data documented in the report into account, synthesis with other studies is possible using the generic inverse variance technique.

Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a washout phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we only used data from the first phase of cross-over studies.

Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary, we simply added these and combined them within the two-by-two table. If data were continuous, we combined data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Where

additional treatment arms were not relevant, we did not reproduce these data.

Dealing with missing data

Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we addressed this within the 'Summary of findings' table by downgrading certainty. Finally, we also downgraded certainty within the 'Summary of findings' table if the loss was between 25% to 50% in total.

Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis (ITT)). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed. We used the rate of those who stayed in the study - in that particular arm of the trial - and applied this to those who did not. We undertook sensitivity analyses to test how prone the primary outcomes were to change when data only from people who completed the study to that point were compared to the ITT analysis using the above assumptions.

Continuous

Attrition

We used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

Standard deviations (SDs)

If SDs were not reported, we tried to obtain the missing values from the authors. If these were not available, where there were missing measures of variance for continuous data, but an exacted standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we calculated SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). When only the SE was reported, SDs were calculated by the formula $SD = SE * \sqrt{n}$. The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2011b). If these formulae did not apply, we calculated the SDs according to a validated imputation method which was based on the SDs of the other included studies (Furukawa 2006). If studies used different scales to measure the same construct, rather than calculate SDs according to the imputation methods, we followed the rules of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) and carried the baseline SDs forward to the missing SDs. Although some of these imputation strategies can introduce error, the alternative would have been to exclude a given study's outcome and thus to lose information.

Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF ([Leon 2006](#)), we felt that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. We therefore did not exclude studies based on the statistical approach used. However, by preference we used the more sophisticated approaches, i.e. we preferred to use MMRM or multiple imputation to LOCF, and we only presented completer analyses if some kind of ITT data were not available at all. Moreover, we addressed this issue in the item 'Incomplete outcome data' of the 'Risk of bias' tool.

Assessment of heterogeneity

Clinical heterogeneity

We considered all included studies without seeing comparison data to judge clinical heterogeneity. We inspected all studies for participants who were outliers or situations that we had not predicted would arise and, where found, discussed such situations or participant groups.

Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We inspected all studies for clearly outlying methods that we had not predicted would arise and discussed any such methodological outliers.

Statistical heterogeneity

Visual inspection

We inspected graphs visually to investigate the possibility of statistical heterogeneity.

Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 statistic alongside the χ^2 P value. We interpreted an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant χ^2 statistic as evidence of substantial heterogeneity ([Deeks 2011](#)). Where substantial levels of heterogeneity were found in the primary outcome, we explored reasons for heterogeneity ([Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results ([Egger 1997](#)). These are described in section 10.1 of the *Cochrane Handbook for Systematic reviews of Interventions* ([Sterne 2011](#)).

Protocol versus full study

We attempted to locate protocols of included RCTs. If the protocol was available, we compared outcomes in the protocol and in the published report. If the protocol was not available, we compared

outcomes listed in the methods section of the trial report with actually reported results.

Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose to use a random-effects model for analyses.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

Standard SEI treatment duration

One of the most vocal arguments for the development of early phase treatments is that there is evidence of a 'critical period' in the early stages of psychosis ([Birchwood 1998](#)). This implies that there may be a dose-response effect for treatment of recent-onset psychosis ([EASY_Extended](#)). The most common duration of SEI treatment given in clinical scenarios is two years, but the duration of treatment given in studies may differ. As a subgroup analysis, where the duration of SEI treatment differed by more than six months from the standard two-year duration of SEI care, we aimed to include only standard duration SEI trials in a subgroup analysis, however all trials were within six months duration of the standard SEI duration, so we did not perform any subgroup analysis.

Investigation of heterogeneity

We reported if inconsistency was high. Firstly, we investigated whether data had been entered correctly. Secondly, if data were correct, we inspected the graph visually and removed outlying studies successively to see if homogeneity was restored. For this review we decided that should this occur with data contributing to the summary finding of no more than 10% of the total weighting, we presented data. If not, we did not pool these data and discussed any issues.

When unanticipated clinical or methodological heterogeneity was obvious, we simply stated hypotheses regarding these for future reviews or versions of this review.

Sensitivity analysis

We carried out sensitivity analyses for primary outcomes only. If there were substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we did not add data from the lower-quality studies to the results of the higher-quality trials, but presented these data within a

subcategory. If their inclusion did not result in a substantive difference, they remained in the analyses.

Implication of randomisation

If trials were described in some way as to imply randomisation, we aimed to compare data from the implied trials with trials that were randomised. However, all our included trials were randomised and therefore we did not conduct this sensitivity analysis.

Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see [Dealing with missing data](#)) we compared the findings when we used our assumption and where we made the comparison with completer data only. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

Assumptions for lost continuous data

Where assumptions had to be made regarding missing SDs (see [Dealing with missing data](#)), we aimed to compare the findings when we used our assumption and where we made the comparison with data that were not imputed. If there was a substantial difference, we aimed to report results and discuss them but continued to employ our assumption. However, we did not need to make any assumptions for lost continuous data and therefore did not conduct this sensitivity analysis.

Risk of bias

We aimed to analyse the effects of excluding trials that were at high risk of bias across one or more of the domains (see [Assessment of risk of bias in included studies](#)), however all trials included at least one domain at high risk of bias so we did not conduct this sensitivity analysis.

Imputed values

We aimed to undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials, but this was not necessary as we did not impute values for ICC in any of the trials.

Fixed- and random-effects

We synthesised data using a random-effects model; however, we also synthesised data for the primary outcome using a fixed-effect model to evaluate whether this altered the significance of the results.

RESULTS

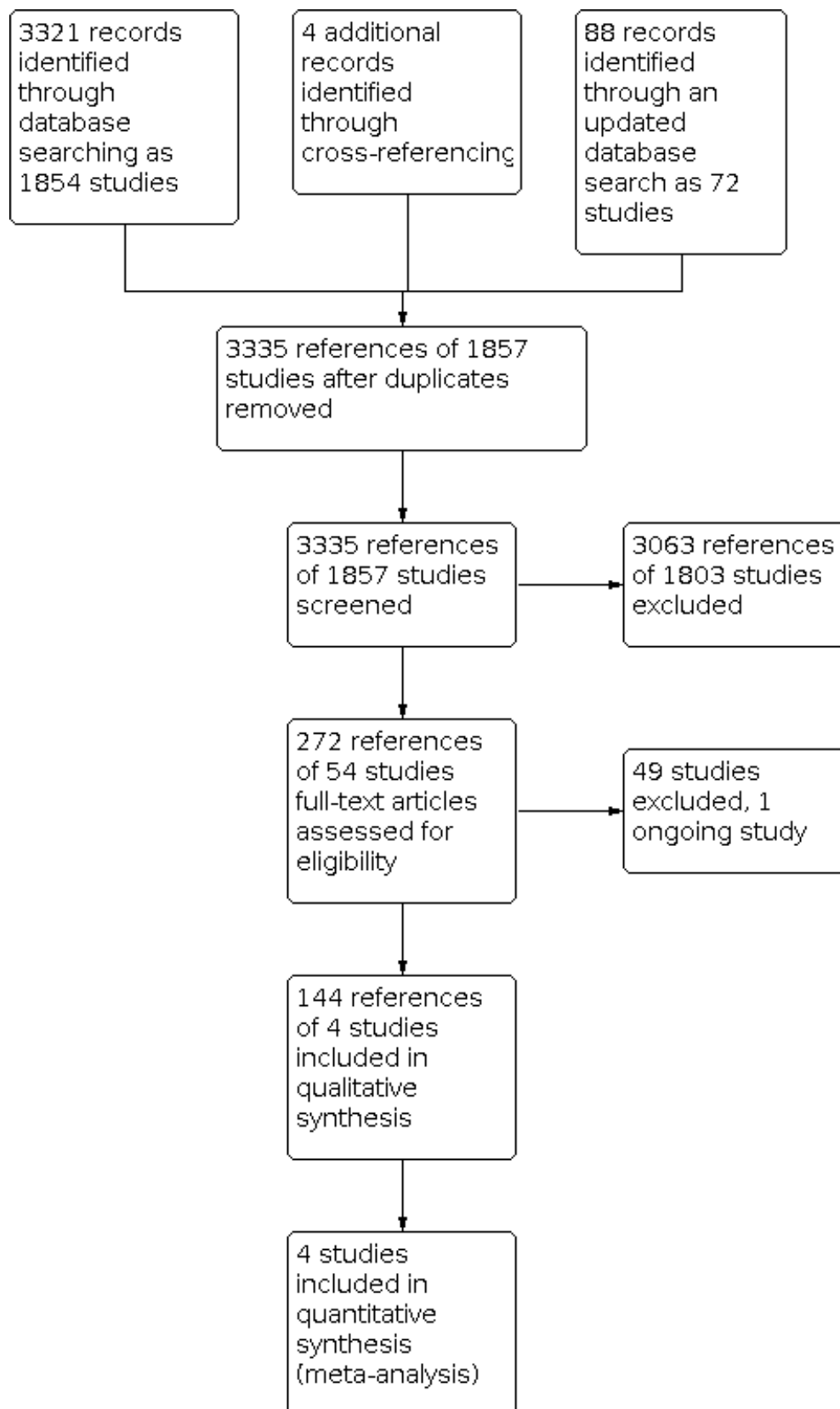
Description of studies

For substantive descriptions of the studies please see [Included studies](#), [Excluded studies](#), and [Ongoing studies](#).

Results of the search

The first electronic search on 3 October 2018 identified 3321 references comprising 1854 studies. The second, updated search on 22 October 2019 identified a further 88 references. We further identified four references but no further studies through a cross-referencing check of relevant papers. After duplicates were removed, 3335 references remained for screening. We excluded 3063 references through inspection of titles and abstracts, and obtained the full texts for the remaining 272 references, comprising 54 studies, to further assess eligibility. We excluded 49 studies; the reasons for exclusion are described in [Excluded studies](#). One trial with three references is in the [Ongoing studies](#) list as the primary outcomes from this study have yet to be published ([JCEP 2010](#)). Overall, we included four trials with 144 references in this review. [Figure 3](#) presents the flow chart of the study screening process.

Figure 3. Study flow diagram.



Included studies

We included four studies with a total of 1145 participants.

Design and duration

Three studies were individually-randomised controlled trials (RCTs) ([LEO](#); [OPUS](#); [OTP](#)), and one was a cluster-RCT ([RAISE](#)). The total treatment duration was 18 months in [LEO](#) and 24 months in [OPUS](#), [OTP](#) and [RAISE](#).

Participants

Diagnosis

In [LEO](#), participants had to meet the diagnostic criteria for non-affective psychotic disorders and they had to be presenting to mental health services for the first time, or presenting to services a second time if on the first presentation they disengaged without receiving treatment.

In [OPUS](#), participants had to meet diagnostic criteria for schizophrenia spectrum disorders, and could not have had more than 12 weeks continuous mental health treatment.

In [OTP](#) participants had to meet the diagnostic criteria for schizophrenia, schizoaffective, or schizophreniform disorders, having only presented to mental health services once (or twice without receiving proper treatment on the first occasion) and having a duration of untreated psychosis of less than 24 months.

In [RAISE](#), participants had to meet diagnostic criteria for non-affective psychosis, excluding substance induced psychotic disorders. They had to be in their first episode of psychosis with less than six months of lifetime antipsychotic prescriptions.

Age and gender

Age limit criteria were as follows: [LEO](#) 16 to 40 years; [OPUS](#) 18 to 45 years; [OTP](#) 18 to 35 years; [RAISE](#) 15 to 40 years. The mean age range in the trials was between 23.1 years ([RAISE](#)) and 26.6 years ([OPUS](#)). The included participants were 405 females (35.4%) and 740 males (64.6%).

Size

The sample size of the included trials ranged from 50 in [OTP](#) to 547 in [OPUS](#), with a total of 1145 participants.

Setting

All four trials took place in community mental health settings in high-income countries ([LEO](#) in England, [OPUS](#) in Denmark, [OTP](#) in Sweden, and [RAISE](#) in the USA).

Interventions

Specialised early intervention (SEI)

[LEO](#) was a SEI service with a multidisciplinary team providing an assertive outreach model of care. It provided an extended hours service (including weekend hours), case management with a case manager/service user ratio of 1:15, and offered a low-dose atypical antipsychotic medication regimen, cognitive behaviour therapy (CBT), family counselling and vocational strategies, all from manualised protocols.

[OPUS](#) was a SEI service with a multidisciplinary team providing an 'enhanced' assertive outreach model of care. The service provided case management for two years, with a caseload ratio of 1:10. The service offered antipsychotic treatment, family psychoeducation, and social skills training.

[OTP](#) was a SEI service with a multidisciplinary treatment team. Case management was offered with a caseload ratio of 1:10 and intensive crisis management if needed. In addition, service users were offered low-dose antipsychotic treatment, structured family psychoeducation, CBT, CBT-based family communication and problem solving skills training.

[RAISE](#) was a standalone SEI service integrated within standard community mental health centres. Treatment was based on four core interventions: medication management, family psychoeducation, resilience-focused individual therapy, and supported employment and education.

Outcomes

Non-scale data

We were able to report dichotomous data on recovery, disengagement, leaving the study for any reason, relapse, admission to psychiatric hospital, number of readmissions to psychiatric hospital, number of days in psychiatric hospital, all-cause mortality, employment, and violent offending.

Recovery was measured in three different ways in the three trials that reported data for the outcome: [LEO](#) defined recovery based on two clinicians' independent review of clinical notes over the course of the 18 months. [OPUS](#) defined recovery as not being psychotic based on the Life Chart Schedule for the two years prior to the five-year follow-up interview. [OTP](#) defined recovery through a clinical composite index based on the absence of 1) psychiatric hospital admissions, minor or major psychotic episode and persistent psychotic symptoms (i.e. four or more on the Brief Psychiatric Rating Scale (BPRS), hallucination or unusual thought content item for six or more consecutive weeks), 2) no suicide attempts, and 3) no poor compliance with treatment, throughout the two-year follow-up period.

Disengagement was measured in three different ways in the three trials that reported data for the outcome: [LEO](#) defined disengagement as having no contact with any mental health service at the 18-month follow-up. [OPUS](#) defined disengagement as stopping treatment despite clinical need according to clinical note review. [OTP](#) defined disengagement as receiving "little or no treatment" throughout the 24-month follow-up period.

We used data for participants leaving the study early for any reason in four trials ([LEO](#); [OPUS](#); [OTP](#); [RAISE](#)). Leaving the study early was defined by any drop out from the study for any reason, including loss to follow-up as reported in the study consort diagram and other supplementary materials. Disengagement relates to leaving treatment from mental health services, while leaving the study for any reason specifically relates to leaving the research study.

Relapse was reported in two studies. [LEO](#) defined relapse based on two clinicians' independent review of clinical notes over the course of the 18 months of treatment from the SEI service. [OTP](#) defined a relapse as either a "major" or a "minor" reoccurrence. We used only major reoccurrence for our data. A major reoccurrence was defined

as a two-point increase in the Target Symptom rating scale and a score of six or seven on one of the key psychotic symptom items on the BPRS scale. In addition, this relapse had to be confirmed by an independent person from the rater (clinical team, or family member) as a significant worsening.

Psychiatric hospital admission was reported in all four trials ([LEO](#); [OPUS](#); [OTP](#); [RAISE](#)). Psychiatric hospital admission was collected at multiple time points in [LEO](#) and [OPUS](#) however, we only used data for time periods measured from randomisation. Results reported in the cluster-RCT [RAISE](#) were adjusted for both site and patient-level random effects and we synthesised these data using the generic inverse variance technique.

The number of admissions was reported as mean psychiatric hospital admissions from randomisation in two trials ([LEO](#); [OTP](#)). The number of psychiatric hospital admission was collected at multiple time points in [LEO](#); however, we only used data for time periods measured from randomisation.

Number of days in psychiatric hospital was reported as mean hospital days per year in three trials ([LEO](#); [OPUS](#); [OTP](#)).

Death - through suicide and natural causes was reported in three studies ([LEO](#); [OPUS](#); [OTP](#)).

Proportion in employment was measured in two studies ([OPUS](#); [RAISE](#)). Results reported in the cluster-RCT [RAISE](#) were adjusted for both site- and patient-level random effects, and we synthesised these data using the generic inverse variance technique.

Violent offending was measured in one study ([OPUS](#)). It measured violent offending by the proportion of 'guilty' verdicts for a violent criminal offence during the two-year and five-year periods of follow-up.

Outcome scales providing usable data

We were able to report outcome scale data on general psychopathology, positive psychotic symptoms, negative psychotic symptoms, depressive symptoms, general functioning, quality of life and service satisfaction.

Mental state scales

- Positive and Negative Syndrome Scale - PANSS ([Kay 1986](#))

PANSS is a 30-item scale including three subscales for measuring the severity of general psychopathology, positive symptoms, and negative symptoms. Each item is rated on a seven-point scale, with higher scores indicating worse outcome. The Positive and Negative sub scales (with seven questions each) have a range of 7 to 49, whilst the general psychopathology subscale (with 16 questions) has a score range of 16 to 112. Two trials reported outcomes on this scale ([LEO](#); [RAISE](#)). Results reported in the cluster-RCT [RAISE](#) were adjusted for both site- and patient-level random effects and we synthesised these data using the generic inverse variance technique.

- Scale for the Assessment of Negative Symptoms - SANS ([Andreasen 1984](#))

The SANS is a valid instrument to assess the negative symptoms of schizophrenia. Each item, of which there are 25, is based on six-point scale, with each domain symptoms rated from 0 (absent) to

5 (severe). Higher scores indicate more symptoms. [OPUS](#) reported outcomes on this scale, using the mean of the five global domain scores (range 0 to 5).

- Scale for the Assessment of Positive Symptoms - SAPS ([Andreasen 2004](#))

SAPS is a rating scale to measure positive symptoms in schizophrenia. The scale is split into four domains, and within each domain separate symptoms are rated from 0 (absent) to 5 (severe). There are a total of 34 items. [OPUS](#) reported outcomes on this scale, using the mean of the four global domain scores (range 0 to 5).

- Brief Psychiatric Rating Scale - BPRS ([Overall 1962](#))

The BPRS is a 24-item scale that measures psychiatric symptoms. Each item is marked on a seven-point Likert scale ranging from one to seven with one being 'not present' and seven being 'extremely severe'. Possible scores range from 24 to 168 with lower scores representing less severe symptoms. Individual questions can be categorised into positive and negative symptoms. [OTP](#) reported outcomes on this scale.

- Calgary Depression Scale - CDS ([Addington 1993](#))

CDS is a 9-item scale designed to measure depression in schizophrenia patients without negative symptoms. The possible score ranges from 0 to 27 with higher scores indicating poor depression state. One trial reported outcomes on this scale ([LEO](#)).

Social functioning scales

- Global Assessment of Functioning - GAF ([Jones 1995](#))

The GAF is a scale to assess psychological, social, and occupational functioning. It is rated on a 100-point scale with lower scores indicating poorer functioning. Three trials report outcomes on this scale ([LEO](#); [OPUS](#); [OTP](#)).

Quality of life scales

- Manchester Short Assessment of Quality of Life - MANSA ([Priebe 1999](#))

MANSA is a self-report questionnaire that comprises 12 items on a seven-point rating scale (range from 12 to 84) assessing satisfaction with life 'in general', with lower scores representing worse functioning. [LEO](#) reported outcomes on this scale; however, items are reversed scored, with lower scores representing better quality of life.

- Heinrichs-Carpenter Quality of Life Scale - QLS ([Heinrichs 1984](#))

The QLS has 21 items rated from semi-structured interview, with each item rated on a seven-point scale, for a total range of 0 to 126. Lower scores represent poorer quality of life. [RAISE](#) reported outcomes on this scale. Results reported in the cluster-RCT [RAISE](#) were adjusted for both site- and patient-level random effects and we synthesised these data using the generic inverse variance technique.

Service satisfaction scales

- The Client Satisfaction Questionnaire - CSQ-8 ([De Wilde 2005](#))

The CSQ-8 is an eight-item self-report of global measure of patient satisfaction with services. The CSQ is substantially correlated with treatment dropout, number of therapy sessions attended, and with change in client-reported symptoms. The CSQ-8 consists of eight items rated on a four-point Likert scale. The items are concerned with quality of services received, how well services met the client's needs and general satisfaction. The total score ranges from eight to 32. Higher scores indicate greater satisfaction of the responders. [OPUS](#) reported outcomes on this scale.

- Verona service satisfaction scale - VSSS ([Ruggeri 1993](#))

The VSSS is a 32-item self-report Likert scale (scored 1 to 5) addressing patients' satisfaction with community-based psychiatric services. Higher scores represent greater satisfaction. [LEO](#) used an eight-item subscale of the VSSS to determine satisfaction with professionals' skills and behaviour, and reverse-scored items so that greater satisfaction was represented by lower scores (scored 8 to 40).

Missing outcomes

The following prespecified outcome was not reported: mental state - clinically important change in general mental state.

Excluded studies

We excluded 47 trials from this review. We have summarised them in [Characteristics of excluded studies](#). The most common reasons for exclusion were that studies did not compare a SEI service in 15 (31.9%) studies, that there was no treatment as usual (TAU) condition in 11 (23.4%) studies, and that the intervention was a psychiatric inpatient-only intervention in six (13.0%) studies.

Ongoing studies

We identified one ongoing trial whose results have not yet been published. Please refer to [Ongoing studies](#) for more details.

Awaiting assessment

No studies were awaiting assessment.

Risk of bias in included studies

See also [Figure 1](#) and [Figure 2](#).

Allocation

We graded three of the four eligible trials (3/4, 75%) as low risk of bias in relation to sequence generation ([LEO](#); [OPUS](#); [OTP](#)). The methods used for sequence generation were either independent or computer-generated sequencing. We graded [RAISE](#) unclear for sequence generation, as it did not describe a method of sequence generation.

Three of the four eligible trials (3/4, 75%) had low risk of bias for allocation concealment ([LEO](#); [OPUS](#); [OTP](#)). All three described some form of allocation concealment through either pre-numbered sealed envelopes or independent central allocation. We graded [RAISE](#) unclear for allocation concealment, as it did not describe a method of allocation concealment.

Blinding

Team-based, long-term treatment interventions are complex care interventions and would be difficult to mask. Therefore, none of

the four trials blinded participants and the treatment team from the treatment arm allocation. We judged that outcome assessment was unlikely to influence results if the primary outcome was an objective outcome (i.e. not a clinical assessment or patient-reported outcome), or if the primary outcome was subjective (i.e. self-rated or interviewer-rated) but those assessing the outcome were blind to the treatment allocation.

We graded all of the four eligible studies as high risk of bias for blinding of the participants. We graded two studies at high risk of bias for blinding of outcome assessments. In [LEO](#), outcome assessors were blind to treatment allocation, however the primary outcome was a subjectively rated outcome made from reading clinical notes of which the outcome assessors were able to guess allocation with 60% accuracy. In [OPUS](#), the primary outcome was an assessor-rated symptom scale and assessors were not blind to treatment allocation.

Incomplete outcome data

We graded three of the four eligible trials (3/4, 75%) as low risk of bias in relation to incomplete outcome data ([LEO](#); [OPUS](#); [OTP](#)). [LEO](#) and [OTP](#) had a low proportion of incomplete outcome data, while [OPUS](#) had 25% missing data at two-year (end of treatment) follow-up in the SEI group and 40% missing data in TAU, but accounted for this using appropriate statistics and sensitivity analyses on the missing data. We rated [RAISE](#) at high risk of bias due to incomplete outcome data. The authors do not report on the exact figures for missing data but 54% in the intervention group and 68% in the TAU group were considered to have missing data either through exiting the study (34% and 53%, respectively), or completing the study with an assessment gap or gaps by missing more than three consecutive assessments in a row (19% and 13%, respectively). While the authors conducted appropriate analyses to account for missing data, we consider that these data were unlikely to be missing at random. We also consider that the difference in missingness between SEI and TAU would likely lead to bias, and no sensitivity analyses were reported in any published literature to test the assumptions of missingness.

Selective reporting

We considered [LEO](#) and [RAISE](#) at low risk of bias for selective reporting. Both trials reported prespecified outcomes from a protocol and there is a consistency of reported outcomes in the protocol, primary papers and follow-up papers. We graded [OTP](#) as unknown risk of bias; we were unable to locate a published protocol, and the trial was registered with a trial registry only after the trial was completed. We graded [OPUS](#) at high risk of bias for selective reporting; their primary outcome is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.

Other potential sources of bias

We did not think there was a high risk of other potential sources of bias within the included trials.

Effects of interventions

See: [Summary of findings 1 Specialised early intervention \(SEI\) compared to treatment as usual \(TAU\) for recent-onset psychosis at end of treatment](#)

Specialised early intervention (SEI) compared to treatment as usual (TAU)

Global state: recovery, as defined by the study

End of treatment

Two trials reported end of treatment recovery data. There was a clear difference between SEI and TAU care groups, favouring SEI (risk ratio (RR) 1.41, 95% confidence interval (CI) 1.01 to 1.97; 2 studies, 194 participants; $I^2 = 18\%$; low-certainty evidence; [Analysis 1.1](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported medium-term recovery data. There was no clear difference between SEI and TAU care groups (RR 0.96, 95% CI 0.71 to 1.30; 1 study, 547 participants; [Analysis 1.1](#)).

Sensitivity analysis, end of treatment

We found no substantive differences when we used data for completers only in a sensitivity analysis (RR 1.40, 95% CI 0.93 to 2.11; 2 studies, 181 participants), or when we used a fixed-effect model instead of a random-effects model (RR 1.41, 95% CI 1.01 to 1.97; 2 studies, 194 participants; [Analysis 1.1](#)).

Service use: disengagement from services, as defined by the study

End of treatment

Three trials reported data on disengagement at the end of treatment. There was a clear difference between SEI and TAU care groups, favouring SEI (RR 0.50, 95% CI 0.31 to 0.79; 3 studies, 630 participants; $I^2 = 0\%$; moderate-certainty evidence; [Analysis 1.2](#)).

Sensitivity analysis, end of treatment

We found no differences when we used data for completers only in a sensitivity analysis (RR 0.50, 95% CI 0.31 to 0.79; 3 studies, 630 participants), or when we used a fixed-effect model instead of a random-effects model in our analysis (RR 0.50, 95% CI 0.31 to 0.79; 3 studies, 630 participants; [Analysis 1.2](#)).

Service use: admission to psychiatric hospital

End of treatment

Four trials reported end of treatment follow-up data for admission to psychiatric hospital. The point estimate suggests a difference between SEI and TAU care groups, favouring SEI, but the 95% confidence interval ranged between favouring SEI and no difference (RR 0.91, 95% CI 0.82 to 1.00; 4 studies, 1145 participants; low-certainty evidence; [Analysis 1.3](#)).

Long-term follow-up (more than 60 months post-treatment)

OTP reported on long-term follow-up data for admission to psychiatric hospital. There was no clear difference between SEI and TAU care groups (RR 0.77, 95% CI 0.48 to 1.24; 1 study, 50 participants).

Service use: readmission to psychiatric hospital

End of treatment

LEO reported data on this outcome. Data for this outcome were presented as 'other data' because of marked skew ([Analysis 1.4](#)), which makes it difficult to interpret the findings.

Long-term follow-up (more than 60 months post-treatment)

OTP reported data on this outcome. Data for this outcome were presented as 'other data' because of marked skew ([Analysis 1.4](#)), which makes it difficult to interpret the findings.

Service use: number of days in psychiatric hospital

End of treatment

Two trials reported data on this outcome. Data for this outcome from the LEO trial were skewed and we excluded it from the analysis. There was a clear difference between SEI and TAU, favouring SEI (mean difference (MD) -27.00, 95% CI -53.68 to -0.32; 1 study, 547 participants; low-certainty evidence; [Analysis 1.5](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OTP reported data on this outcome. We excluded data for this outcome from the analysis.

Global state: relapse, as defined by study

End of treatment

Two trials reported end of treatment relapse data. There was no clear difference between SEI and TAU care groups (RR 0.71, 95% CI 0.47 to 1.08; 2 studies, 194 participants; $I^2 = 0\%$; low-certainty evidence; [Analysis 1.6](#)).

Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, general psychotic symptoms

End of treatment

Two trials reported data on this outcome. There was no clear difference between SEI and TAU care groups (standardised mean difference (SMD) -0.41, 95% CI -4.58 to 3.75; 2 studies, 304 participants; very low-certainty evidence; [Analysis 1.7](#)).

Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, positive psychotic symptoms

End of treatment

Four trials reported data for average endpoint scores on specific symptom mental state scales. There was a clear difference between SEI and TAU groups, favouring SEI (SMD -0.18, 95% CI -0.33 to -0.03; 4 studies, 723 participants; [Analysis 1.8](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported medium-term endpoint score data on positive psychotic symptoms. There was no clear difference between SEI and TAU care groups (SMD 0.06, 95% CI -0.16 to 0.29; 1 study, 301 participants).

Long-term follow-up (more than 60 months post-treatment)

OPUS reported long-term endpoint score data on positive psychotic symptoms. There was no clear difference between SEI

and TAU care groups (SMD 0.02, 95% CI -0.15 to 0.19; 1 study, 547 participants).

Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, negative psychotic symptoms

End of treatment

Four trials reported data for average endpoint scores on specific symptom mental state scales. There was a clear difference between SEI and TAU groups, favouring SEI (SMD -0.32, 95% CI -0.53 to -0.11; 4 studies, 723 participants; [Analysis 1.9](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported medium-term endpoint score data on negative psychotic symptoms. There was no clear difference between SEI and TAU care groups (SMD -0.07, 95% CI -0.29 to 0.16; 1 study, 301 participants).

Long-term follow-up (more than 60 months post-treatment)

OPUS reported long-term endpoint score data on negative psychotic symptoms. There was no clear difference between SEI and TAU care groups (SMD 0.05, 95% CI -0.12 to 0.21; 1 study, 547 participants).

Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, depressive symptoms

End of treatment

LEO reported data on this outcome. There was no clear difference between SEI and TAU care groups (MD 0.00, 95% CI -1.35 to 1.35; 1 study, 99 participants; very low-certainty evidence; [Analysis 1.10](#)).

Behaviour: specific, occurrence of violent incidents (to self, others or property)

End of treatment

OPUS reported data on occurrence of violent incidents at end of treatment. There was no clear difference between SEI and TAU care groups (RR 0.99, 95% CI 0.38 to 2.60; 1 study, 547 participants; very low-certainty evidence; [Analysis 1.11](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported data on occurrence of violent incidents at medium-term follow-up. There was no clear difference between SEI and TAU care groups (RR 0.93, 95% CI 0.47 to 1.84; 1 study, 547 participants).

Adverse effects/events: death, suicide or natural cause

End of treatment

Three trials reported on all-cause mortality at end of treatment. There was no clear difference between SEI and TAU care groups (RR 0.21, 95% CI 0.04 to 1.20; 3 studies, 741 participants; $I^2 = 0\%$; low-certainty evidence; [Analysis 1.12](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

Two trials reported on all-cause mortality at medium-term follow-up. There was no clear difference between SEI and TAU care groups (RR 0.56, 95% CI 0.22 to 1.46; 2 studies, 691 participants; $I^2 = 0\%$).

Long-term follow-up (more than 60 months post-treatment)

OTP reported data on all-cause mortality at long-term follow-up. There was no clear difference between SEI and TAU care groups (RR 0.23, 95% CI 0.01 to 5.28; 1 study, 50 participants).

Leaving the study early: for any reason

End of treatment

Four trials reported end of treatment data on leaving the study early. There was a clear difference between SEI and TAU care groups, favouring SEI (RR 0.63, 95% CI 0.54 to 0.74; 4 studies, 1145 participants; $I^2 = 0\%$; moderate-certainty evidence; [Analysis 1.13](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported medium-term follow-up data on leaving the study early. There was no clear difference between SEI and TAU (RR 1.00, 95% CI 0.86 to 1.16; 1 study, 547 participants).

Quality of life: recipient, overall, average endpoint score on quality of life scale

End of treatment

Two trials reported end of treatment data on average endpoint scores on quality of life scales. There was no clear difference between SEI and TAU (SMD 0.26, 95% CI -0.08 to 0.60; 2 studies, 300 participants; [Analysis 1.14](#)).

Functioning: general, average endpoint score on general functioning scale

End of treatment

Two trials reported on end of treatment data on average endpoint score on a general functioning scale. There was a clear difference between SEI and TAU, favouring SEI (SMD 0.37, 95% CI 0.07 to 0.66; 2 studies, 467 participants; $I^2 = 45\%$; low-certainty evidence; [Analysis 1.15](#)).

Medium-term SEI follow-up (1 to 60 months post-treatment)

OPUS reported on medium-term follow-up data on average endpoint score on a general functioning scale. There was no clear difference between SEI and TAU (SMD 0.07, 95% CI -0.16 to 0.29; 1 study, 301 participants).

Long-term SEI follow-up (more than 60 months post-treatment)

OPUS reported on long-term follow-up data on average endpoint score on a general functioning scale. There was no clear difference between SEI and TAU (SMD -0.02, 95% CI -0.19 to 0.14; 1 study, 547 participants).

Functioning: specific, any change in education or employment status

End of treatment

Two trials reported end of treatment data on change in employment statuses. There was no clear difference between SEI and TAU (RR 1.21, 95% CI 0.94 to 1.55; 2 studies, 951 participants; [Analysis 1.16](#)).

Satisfaction with care: recipient, average endpoint score on satisfaction scale

End of treatment

Two trials reported end of treatment data on an average endpoint score on a satisfaction scale. There was a clear difference between SEI and TAU, favouring SEI (SMD 0.69, 95% CI 0.51 to 0.88; 2 studies, 463 participants; $I^2 = 0\%$; low-certainty evidence; [Analysis 1.17](#)).

DISCUSSION

Summary of main results

This review included three individually-randomised controlled trials (RCTs) ([LEO](#); [OPUS](#); [OTP](#)), and one cluster-RCT ([RAISE](#)), that investigated the effectiveness of standalone community mental health teams called specialised early intervention (SEI) in improving outcomes for people with first and early psychosis in comparison to treatment as usual (TAU).

Overall we found low-certainty evidence that SEI increased the number of people considered recovered at the end of treatment, and moderate-certainty evidence that fewer people had disengaged from SEI treatment than TAU. At medium-term follow-up of between 1 and 60 months after treatment had ended, we did not find any clear difference in recovery between SEI and TAU, although this included data from only one trial. No trials published data on medium-term disengagement or long-term (longer than 60 months after the intervention had ended) recovery or disengagement.

We found a number of differences between SEI and TAU for our secondary outcomes at end of treatment, although most of these were of between very low- and moderate-certainty evidence. There was a clear, but small, effect of fewer admissions to psychiatric hospital favouring SEI, and small effects for fewer reported positive (hallucinations, delusions and disordered thinking) and negative (social withdrawal, flat or blunted affect, and poverty of speech) psychotic symptoms and better general functioning, all favouring SEI. Participants in SEI treatment also reported higher satisfaction with their care. Where trials reported medium-term (positive and negative symptoms, general functioning) or long-term (admission to hospital, positive and negative symptoms, and general functioning) data, we no longer found a difference between SEI and TAU. We found no clear differences at end of treatment, or medium- or long-term outcomes (where reported), for relapse, general psychotic symptoms, depressive symptoms, occurrence of violent incidents, death from suicide or natural causes, quality of life, or change in employment or educational status.

Overall completeness and applicability of evidence

Completeness

We know of no further trials of SEI planned or underway other than the one identified in the [Ongoing studies](#). There were a limited number of eligible trials for this review, although included trials did tend to collect similar outcome measures at end of treatment. There was a lack of completeness in the medium (1 - 60 months after intervention ended) or long-term (more than 60 months after intervention ended) follow-ups, with only a single trial available for most outcome comparisons. There were a number of other trials of SEI which were ineligible due to their sample, which did not meet our criteria for a service to be considered 'early intervention' (a

duration of untreated psychosis of less than three years and equal to or fewer than two episodes of psychosis). Another well-known trial of SEI was not eligible as it did not offer a standalone SEI service ([GET UP PIANO 2013](#)).

Applicability

All four included trials recruited participants with early psychosis who would be eligible for SEI services. There were slight differences in recruitment criteria, with two trials specifically recruiting 'first episode' patients with little or no previous treatment ([OPUS](#); [RAISE](#)), and two trials recruiting from an 'early psychosis' population who had one or two episodes of psychosis, but with minimal treatment for the first episode. Duration of untreated psychosis differed markedly between trials, and with large variation within each trial, but this would also be expected in everyday clinical practice. Each trial differed slightly in the treatment given, but all adhered to an assertive outreach approach within a standalone team.

All trials were conducted in high-income countries. Therefore this evidence may not apply to SEI given in low- or middle-income countries.

Certainty of the evidence

The certainty of evidence ranged between moderate and very low across our collected outcomes. When all four trials reported data on the same outcome, the evidence became of far higher certainty and met the optimal information size criteria. When there were fewer data to pool, this led to outcomes with imprecise estimates or outcomes being below the threshold for optimal information size. All four included trials were at high risk of bias in at least one domain of the Cochrane 'Risk of bias' tool. We downgraded all trials on risk of bias due to lack of blinding. This may be considered a controversial decision, as being able to blind participants in a complex intervention health services trial would be difficult, if not impossible. This risk could be minimised by appropriately blinding the assessment of outcomes, of which only two of the four trials adequately achieved. Finally, incomplete reporting of trial characteristics, such as randomisation procedures limited our ability to rate risk of bias in the two trials.

Potential biases in the review process

We have used a comprehensive search strategy with no language, date, or publication restrictions. However, there is always a possibility that eligible trials were missed. The SEI team construct is not stringently defined, and as such, disagreement about what qualifies as SEI treatment is possible. We aimed to adhere to a strict interpretation of SEI, including stringent eligibility criteria for participants and for the team structure.

Finally, we were unable to obtain some missing outcome data from eligible studies, as they were not reported or not available from study authors on request, which may have biased the results.

Agreements and disagreements with other studies or reviews

There is one previous review from the Cochrane Library, that included a comparison between SEI and TAU for early psychosis. [Marshall 2011](#) included one eligible trial and found preliminary evidence for the effectiveness of SEI services. The [Marshall 2011](#) trial differed markedly in scope to our current review.

They reviewed all treatments for early psychosis, including early detection studies and treatments for those in the prodromal phase of psychosis, along with treatments for people with a first episode of psychosis. In comparison, our review only compared SEI community health services for people with recent-onset psychosis. They included one eligible trial and found preliminary evidence for the effectiveness of SEI services.

There is one other notable review of SEI. [Correll 2018](#) conducted a systematic review and meta-analysis of SEI versus TAU for early phase psychosis and included 10 studies. Our review included fewer studies due to different eligibility criteria. We specified both a time since onset criteria and a number of psychotic episodes criteria for study participants. We also only included studies that evaluated SEI interventions that operated as an independent team, rather than as an enhanced care package within an existing community mental health team. Treatment given by SEI teams within the 10 included studies in the [Correll 2018](#) review differed markedly. Results of our review and [Correll 2018](#) were similar; with both finding more service users in recovery in SEI, fewer discontinuing treatment, fewer hospitalised at end of treatment, lower reported positive and negative psychotic symptoms, and better global functioning. [Correll 2018](#) found no difference in general psychotic symptoms and depressive symptoms at the 18- to 24-month end of treatment time points, results that are similar to our own end of treatment findings. Our results differed to [Correll 2018](#) in regards to quality of life, numbers in work, and relapse, all outcomes of which they found differences between SEI and TAU (in favour of SEI) but we did not.

AUTHORS' CONCLUSIONS

Implications for practice

For people with psychosis

There is some support for the effectiveness of SEI services while a person is being treated by them. There is low-certainty evidence that treatment from a SEI team in comparison to TAU results in fewer admissions to psychiatric hospital and moderate-certainty evidence it leads to fewer disengagements from community mental health treatment. There is also moderate-certainty evidence that SEI treatment results in fewer positive (hallucinations, delusions and disordered thinking) and negative (social withdrawal, flat or blunted affect, and poverty of speech) psychotic symptoms and low-certainty evidence of greater satisfaction with care during treatment. There is low-certainty evidence that it also improves general functioning and the likelihood of recovery during treatment. Apart from disengagement from services and satisfaction with services, these effects are generally small and may not be clinically meaningful. There is also no evidence that after the treatment has finished, that these benefits are maintained.

As it is generally accepted that people in the early stages of psychosis require mental health treatment and there is no evidence of harm from SEI treatment in comparison to TAU, nor evidence of superior models of health care, SEI may provide some benefit.

For clinicians

There is low-certainty evidence for the use of SEI services in comparison to TAU for a small reduction in psychiatric hospitalisation, and moderate-certainty evidence of a large effect of reduction in disengagement from mental health services. There

is moderate-certainty evidence that SEI results in a small reduction of positive (hallucinations, delusions and disordered thinking) and negative symptoms (social withdrawal, flat or blunted affect, and poverty of speech) and low-certainty evidence that it greatly increases satisfaction in care, while there is low-certainty evidence that it improves general functioning and the likelihood of recovery. These effects were only observed during treatment and there was no evidence that outcomes are improved after the treatment has finished, although these were based on only one trial.

The evidence described here only applies for people with first- or second-episode psychosis treated within three years of start of their symptoms, who have had little or no previous treatment for their psychosis. This evidence also only applies to SEI services that provide a standalone service as an independent package of care, rather than an add-on to the currently available community mental health care (TAU).

For policy makers

For policy makers with the ability to implement SEI treatment programmes, there is between low- and moderate-certainty evidence that there are short-term clinical benefits to implementing SEI services in high-income countries. Service-level benefits include a reduction in admissions to psychiatric hospital and low-certainty evidence of a reduction in the number of days spent in psychiatric hospital. Implementing SEI may improve service efficiency and reduce costs, although this review did not attempt to measure the economic impact of SEI services.

All four included trials came from high-income countries. There is no evidence for SEI compared to TAU services in middle- and low-income countries.

Implications for research

General

While there were a small number of eligible trials, the size of the trials meant that optimal information criteria was generally met. All trials were at high risk of bias in at least one 'Risk of bias' item, in particular 'blinding of participants and personnel' in all four trials and 'blinding of outcome assessment' in two. As it is unlikely that one could find a suitable method of blinding SEI treatment from participants and personnel, it makes blinding the outcomes assessment all the more important. Participants leaving the study early was also high across trials, between 0% and 53.6% by trial arm (overall participants leaving the study early across all studies 34.5%, $n = 1145$). There were also no trials of SEI conducted in middle- or lower-income countries, and both SEI and TAU probably differ in middle- or lower-income countries, as well as potential differences in referral to these services (and therefore the types of participants who would be recruited for trials of SEI versus TAU). We did not collect outcome data on compulsory treatment or use of mental health legislation, which is an important outcome and should be included in any future studies and reviews. We have included a suggested design of a future trial of SEI in [Table 1](#).

Specific

If further trials of SEI are conducted, we would recommend large, high-quality trials that minimise risk of bias according to CONSORT, and trials in lower- or middle-income countries. The priority for any trial should be establishing the medium- and long-term outcomes of SEI after treatment has ended, as there is currently insufficient

data to make any inference on these outcomes. Trials would need to be conducted in regions where there was still clinical equipoise as it is unlikely this equipoise exists in regions with well-established SEI services.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

LEO

Study characteristics

Methods	<p>Study design: individually-RCT</p> <p>Duration: intervention of 18 months, follow-up until end of treatment at 18 months, and 5-year follow-up</p> <p>Setting: community-based mental health team, England</p> <p>Recruitment method: patients who had presented to secondary mental health services (either through inpatient psychiatric services or community referrals) for first time, or presenting for a second time after a first presentation but subsequent disengagement</p>
Participants	<p>Diagnosis: diagnosis of non-affective psychosis</p> <p>N = 144</p> <p>Age: median age at baseline = 25 (IQR = 21.0 to 25.0)</p> <p>Sex: n = 93 (64.6%) male</p> <p>Inclusion criteria: aged 16 to 40, first or second presentation to mental health services specifically for treatment of non-affective psychosis</p> <p>Exclusion criteria: organic psychosis, primary substance misuse diagnosis, asylum seekers liable to enforced dispersal</p>
Interventions	<ul style="list-style-type: none"> • Assertive outreach • Low-dose antipsychotics • CBT • Family counselling • Vocational support
Outcomes	<ul style="list-style-type: none"> • Recovery (2 clinicians' independent review of clinical notes over the course of the 18 months) • Relapse (2 clinicians' independent review of clinical notes over the course of the 18 months) • Readmission • Number of admissions to psychiatric hospital • Number of days in hospital (skewed data) • General psychotic symptoms - PANNS - modified • Positive symptoms - PANNS • Negative symptoms - PANNS • Depressive symptoms - CDG • All-cause mortality • Quality of life - MANSA • General functioning - GAF • Service satisfaction - Verona satisfaction scale
Notes	<p>Funding source: Directorate of Health and Social Care London research and development organisation and management programme (grant number RDC 01567)</p> <p>Conflicts of interest: TC and PP have received support from Eli Lilly, AstraZeneca, Janssen-Cilag and Novartis for AstraZeneca, Janssen-Cilag and Novartis for attending and speaking at conferences.</p>

Risk of bias

LEO (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomised to specialised care or standard care by permuted random blocks of between two and six. Group allocation was concealed in sealed envelopes. The trial statistician (GD) independently carried out the randomisation and concealment of results." Judgement: random permuted blocks
Allocation concealment (selection bias)	Low risk	Quote: as above Judgement: sealed envelopes, suggestive of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blind to allocation, and subjective primary outcome rated by assessors who were able to guess allocation arm with above chance accuracy. Raters conducting participant interviews were not blind to allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Group allocation remained concealed until completion of the ratings. To test the success of blinding, assessors guessed the group allocation of each patient. The two raters correctly guessed the allocation of 60% (95% confidence interval 52% to 63%) of the patients (κ 0.20)" Judgement: assessors blinded and carried out ratings on extracts from notes with information about group allocation had been removed but could guess with above chance 60% accuracy. Secondary outcomes data from participant interviews were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: low proportion of missing outcome data, carried out intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Judgement: primary outcomes reported according to trial registry ISRCTN73679874
Other bias	Low risk	None

OPUS
Study characteristics

Methods	<p>Study design: individually-RCT</p> <p>Duration: intervention of 24 months, follow-up until end of treatment at 24 months, and 5-year and 10-year follow-up</p> <p>Setting: community-based mental health team, Denmark</p> <p>Recruitment method: patients who had presented to secondary mental health services (either through inpatient psychiatric services or community referrals) for the first time and having no more than 12 weeks of antipsychotic treatment</p>
Participants	<p>Diagnosis: diagnosis of schizophrenia spectrum disorders, with diagnosis of schizophrenia comprising n = 382 (69%) of sample</p> <p>N = 547</p> <p>Age: mean age at baseline 26.6 (SD = 6.4) and 26.6 (SD = 6.3) for intervention and TAU, respectively</p> <p>Sex: n = 323 (59.0%) male</p>

OPUS (Continued)

Inclusion criteria: aged 18 to 45 years, first contact with mental health services

Exclusion criteria: prescribed antipsychotic medication for more than 12 weeks of continuous treatment

Interventions	<ul style="list-style-type: none"> Enhanced assertive outreach model of care for two years, with a caseload ratio a 1:10 Antipsychotic treatment Family psychoeducation Social skills training
Outcomes	<ul style="list-style-type: none"> Recovery - not being psychotic based on the Life Chart Schedule for the two years prior to the five-year follow-up interview Leaving the study for any reason Readmission Number of days in psychiatric hospital Positive symptoms - SAPS Negative symptoms - SANS All-cause mortality General functioning - GAF In employment or education Service satisfaction - satisfaction questionnaire
Notes	<p>Funding source: Danish Ministry of Health (jr.nr. 96-0770-71), Danish Ministry of Social Affairs, University of Copenhagen, Copenhagen Hospital Corporation, Danish Medical Research Council (jr.nr. 9601612 and 9900734), and Slagtermester Wørzners Foundation.</p> <p>Conflicts of interest: none declared</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The included patients were centrally randomised to integrated treatment or standard treatment. In Copenhagen, randomisation was carried out through centralised telephone randomisation at the Copenhagen Trial Unit. The allocation sequence was computer generated, 1:1, in blocks of six, and stratified for each of five centres. In Aarhus, the researchers contacted a secretary by telephone when they had finished the entry assessment of each patient. The secretary then drew one lot from among five red and five white lots out of a black box. When the block of 10 was used, the lots were redrawn. Block sizes were unknown to the investigators."</p> <p>Judgement: randomly allocated by independent researcher</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: as above</p> <p>Judgement: central allocation, adequate concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Participants and personnel not blind to allocation, and subjective primary outcome rated by assessors who were not blind to allocation arm.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Quote: "Only independent investigators (PiJ, MA, PK, RM, LP,AT, TC, JØ) were involved in follow-up interviews. For practical reasons, they could not be kept blind to treatment allocation"</p>

OPUS (Continued)

		Judgement: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding due to it being an assessment by interviewer.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: missing data have been imputed using appropriate methods
Selective reporting (reporting bias)	High risk	One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified. Specifically the change in specified primary outcome was reported, but the original primary outcome result not reported.
Other bias	Low risk	None

OTP
Study characteristics

Methods	<p>Study design: individually-RCT</p> <p>Duration: intervention of 24 months, follow-up until end of treatment at 24 months, 10-year follow-up</p> <p>Setting: community-based mental health team, Norway</p> <p>Recruitment method: consecutive referrals to secondary mental health services (either through inpatient psychiatric services or community referrals) for the first time and having no more than 24 months of previous psychiatric treatment</p>
Participants	<p>Diagnosis: diagnosis of schizophrenia and related disorders as per DSM-IV</p> <p>N = 50</p> <p>Age: mean age at baseline = 25.4 (SD = 4.6)</p> <p>Sex: n = 31 (62%) male</p> <p>Inclusion criteria: aged 18 to 35, first or second episode of psychosis</p> <p>Exclusion criteria: more than two years duration since first onset of symptoms, primary substance misuse diagnosis, mental retardation, not residing in service area during the study</p>
Interventions	<ul style="list-style-type: none"> • Stand-alone multidisciplinary team 10:1 caseload • Medication • Structured family psychoeducation • CBT • Family communication and problem solving • Home crisis management • Individual CBT strategies for symptoms
Outcomes	<ul style="list-style-type: none"> • Recovery - a clinical composite index based on the absence of: <ul style="list-style-type: none"> * psychiatric hospital admissions, minor or major psychotic episode and persistent psychotic symptoms (i.e. 4 or more on the BPRS hallucination or unusual thought content item for six or more consecutive weeks) * no suicide attempts * no poor compliance with treatment, throughout the two-year follow-up period • Relapse - a two-point increase in the Target Symptom rating scale and a score of six or seven on one of the key psychotic symptom items on the BPRS. In addition, this relapse had to be confirmed by an independent person from the rater (clinical team, or family member) as a significant worsening.

OTP (Continued)

- Leaving the study for any reason
- Readmission
- Number of admissions to psychiatric hospital
- Number of days in hospital
- Positive symptoms - BPRS
- Negative symptoms - BPRS
- All-cause mortality
- General functioning - GAF

Notes

Funding source: Norwegian Research Council and the Norwegian Ministry of Health

Conflict of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A secretary who was not part of the clinical service opened prenumbered envelopes with treatment group assignment according to random numbers provided by the central Optimal Treatment Project administration. Blocks were of variable size (8–12), stratified according to sex and with a ratio of IT to ST of 3: 2 to ensure that the majority of cases received the experimental treatment." Judgement: the investigators adequately describe a randomly allocated sequence by independent researcher
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly allocated to Integrated Treatment (IT), or ST, by an independent assistant with no knowledge of the referred patients" Judgement: low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: participants and personnel not blind to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Ratings were made by an independent rater who was blind to treatment conditions and trained to obtain a 0.8 kappa coefficient of inter-rater reliability on all rating scales." Judgement: low risk of detection bias, although authors do not report on number of participants who's blinding could be guessed by assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "Missing data were less than 10%"; Judgement: for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size
Selective reporting (reporting bias)	Unclear risk	No available registered protocol, trial registry lacks complete outcome information, trial registry entry after trial complete. Therefore unable to determine whether selective reporting occurred.
Other bias	Low risk	None

RAISE

Study characteristics

Methods	<p>Study design: cluster-RCT, with clusters at the team level</p> <p>Duration: intervention of 24 months, follow-up until end of treatment at 24 months</p> <p>Setting: community-based mental health team, USA</p> <p>Recruitment method: participants who were taken on to the caseloads of the community teams who met eligibility criteria and consented to the intervention</p>
Participants	<p>Diagnosis: DSM-IV diagnoses of schizophrenia $n = 214$ (52.9%), schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified were included</p> <p>$N = 404$; 34 randomised community teams (SEI = 17 team, TAU = 17 teams)</p> <p>Age: mean age at baseline 23.2 (SD = 5.2) and 23.1 (SD = 4.9) for intervention and TAU, respectively</p> <p>Sex: $n = 293$ (72.5%) male</p> <p>Inclusion criteria: aged 15 to 40, a first episode of psychosis, less than six months of lifetime psychotic medications</p> <p>Exclusion criteria: diagnosis of affective psychosis, substance-induced psychotic disorder, organic psychosis, clinically significant head trauma or serious medical condition, non-English language</p> <p>The participants in the SEI team differed from those in the TAU team by sex (77.6% male in comparison to 66.2%), had fewer participants with a previous hospitalisation (76.3% versus 81.6%) and worse symptom scores and fewer attending school than those in the TAU teams.</p>
Interventions	<ul style="list-style-type: none"> • NAVIGATE, components: COMPASS (individualised medication management assisted by computer decision support system) • Family education • Individual resiliency training • Supported education and employment
Outcomes	<ul style="list-style-type: none"> • Readmission, • General psychotic symptoms - BPRS • Positive symptoms - BPRS • Negative symptoms - BPRS • Quality of life - Heinrichs Carpenter Quality of Life Scale • Leaving the study for any reason • In employment or education
Notes	<p>Funding source: American Recovery and Reinvestment Act, NIMH (grant number HHSN271200900019C), NIMH Advanced Centers for Intervention and/or Services Research award (P30MH090590).</p> <p>Conflicts of Interest: Dr. Kane has been a consultant for Alkermes, Amgen, Bristol-Myers Squibb, Eli Lilly, EnVivo Pharmaceuticals (Forum), Forest, Genentech, H. Lundbeck, Intra-Cellular Therapies, Janssen Pharmaceutica, Johnson and Johnson, Merck, Novartis, Otsuka, PierreFabre, Reviva, Roche, Sunovion, and Teva; he has received honoraria for lectures from Bristol-Myers Squibb, Genentech, Janssen, Lundbeck, and Otsuka; and he is a shareholder in MedAvante and in Vanguard Research Group. Dr. Robinson has been a consultant to Asubio, Otsuka, and Shire; and he has received grants from Bristol-Myers Squibb, Janssen, and Otsuka. Dr. Schooler has served on advisory boards or as a consultant for Abbott, Alkermes, Amgen, Eli Lilly, Forum (formerly EnVivo), Janssen Psychiatry, Roche, and Sunovion; she has received grant or research support from Genentech, Neurocrine, and Otsuka; and she has served on a data monitoring board for Shire and on the faculty of the Lundbeck International Neuroscience Foundation. Dr. Brunette has received grant support from Alkermes. Dr. Correll has been a consultant</p>

RAISE (Continued)

or adviser to or has received honoraria from AbbVie, Actavis, Actelion, Alexza, Alkermes, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, Intra-Cellular Therapies, Janssen, Johnson and Johnson, Lundbeck, MedAvante, Medscape, Merck, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda; and he has received grant support from Bristol-Myers Squibb, Janssen, Johnson and Johnson, Novo Nordisk, Otsuka, and Takeda. Ms Marcy is a shareholder in Pfizer. Mr Robinson has received grant support from Otsuka and is a shareholder in Pfizer. Dr Kurian has received grant support from Evotec, Forest, Johnson and Johnson, Naurex, Pfizer, Rexahn, and Targacept. Dr Miller has received payments for serving on a data monitoring committee for a study sponsored by Otsuka. The authors and their associates provide training and consultation about implementing NAVIGATE treatment that can include compensation. Dr Meyer-Kalos, Dr Glynn, and Dr Robinson had received compensation for these activities. The other authors report no financial relationships with commercial interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Clinics were randomly assigned to the experimental intervention (N=17) or to standard care (N=17). None withdrew after randomisation" Judgement: authors state that clusters were randomly allocated but provide no detail on the method of sequence generation in protocol or outcome papers.
Allocation concealment (selection bias)	Unclear risk	Judgement: no text detailing allocation concealment in protocol or outcome papers.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement: participants and personnel not blind to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Centralized assessors, who were masked to individual treatment assignments and overall study design, administered..." Judgement: we considered that these centralised assessors conferred a low risk of bias for blinding of outcome assessment, however the authors do not detail whether there was any unbinding by assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement: analysis corrects for missing data, however there were extensive missing data: 51% of sample completed follow-up, 55% in TAU and 45% in SEI respectively. Authors do not state overall proportion of missing data for repeated measures. It is likely that this missing data are not missing at random and missingness is likely to produce bias. We could find no evidence of sensitivity analyses examining missing data assumptions.
Selective reporting (reporting bias)	Low risk	Consistency of stated outcomes in trial registry and outcome papers.
Other bias	Low risk	None

BPRS: Brief Psychiatric Rating Scale

CBT: cognitive behaviour therapy

CDG: congenital disorders of glycosylation

GAF: Global Assessment of Functioning

IQR: interquartile range

MANSA: Manchester Short Assessment of Quality of Life

NAVIGATE: A comprehensive early treatment program for people with first episode psychosis

PANSS: Positive and Negative Syndrome Scale

RCT: randomised controlled trial

SAPS: Scale for the Assessment of Positive Symptoms

SANS: Scale for the Assessment of Negative Symptoms

SD: standard deviation

SEI: specialised early intervention

TAU: treatment as usual

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alaghband-Rad 2006	Intervention: not a SEI service
Cai 2013	Intervention: medication trial
Carpenter 1982	Intervention: medication trial
Cechnicki 2017	Intervention: no minimum duration of untreated psychosis. Not a standalone service
Chen 2013	Intervention: inpatient population, not community healthcare team intervention
COAST 2004	Intervention: not within three years of onset of illness
Dai 2007	Intervention: inpatient population, not community healthcare team intervention
EASY_Extended	Comparator: no TAU
Fan 2005c	Intervention: not a SEI service
GET UP PIANO 2013	Intervention: not a standalone service
Hansen 2012	Comparator: no TAU
Hou 2007	Intervention: inpatient population, not community healthcare team intervention
ISRCTN58681229	Comparator: no TAU
J-CAP 2014	Intervention: not within three years of onset of illness
LEO-CAT 2004	Intervention: not a SEI service evaluation, early detection only
Li 2012a	Intervention: inpatient population, not community healthcare team intervention
Li 2012b	Intervention: not a SEI service
Linszen 1994	Comparator: no TAU
Linszen 2002	Comparator: no TAU
Linszen 2003	Comparator: no TAU
Linszen 2006	Comparator: no TAU
Linszen 2007	Comparator: no TAU
Liu 2012a	Intervention: medication trial

Study	Reason for exclusion
Liu 2012b	Intervention: not a SEI service
Malla 2000	Randomisation: not a RCT
Malla 2017	Intervention: extended SEI versus standard SEI, no TAU
NCT01783457	Comparator: no TAU
NCT01936220	See Linszen 2007
NCT02037581	Randomisation: not a RCT
NCT02751632	Comparator: no TAU
NCT03409393	Intervention: not a SEI service
OPUS II	Intervention: extended SEI versus standard SEI, no TAU
Pan 2012	Intervention: not a SEI service
Qi 2006	Intervention: not a SEI service
Qu 2012	Intervention: medication trial
Rosenbaum 2002	Randomisation: not a RCT
Santos 2008	Intervention: not a SEI service
Sharivar 2010	Intervention: not a SEI service
Sheng 2009	Intervention: inpatient population, not community healthcare team intervention
STEP 2012	Intervention: not within three years of onset of illness
Sun 2010	Intervention: not a SEI service
Tang 2012	Intervention: inpatient population, not community healthcare team intervention
Valencia 2010	Intervention: not a SEI service
Valencia 2012	Intervention: not a SEI service
Valencia 2013	Intervention: not a SEI service
Wan 2012	Intervention: medication trial
Wang 2012	Intervention: not a SEI service
Zhang 2009	Intervention: not a SEI service
Zipursky 2004	Comparator: no TAU

RCT: randomised controlled trial
SEI: specialised early intervention
TAU: treatment as usual

Characteristics of ongoing studies [ordered by study ID]

JCEP 2010

Study name	Stage-specific case management for early psychosis
Methods	Study design: individually-randomised controlled trial Country: Hong Kong Setting: community-based mental health team
Participants	Eligibility criteria: 22 - 25 years of age, with a diagnosis of: <ul style="list-style-type: none"> • schizophrenia; • schizophreniform disorder; • schizoaffective disorder; • delusional disorder; • brief psychotic disorder; • psychotic disorder not otherwise specified; • manic episodes with psychosis; • Cantonese speaking • No more than 12 months of treatment following presentation for first episode psychosis • Ability to give consent • Absence of organic brain injury
Interventions	Components of treatment included: <ul style="list-style-type: none"> • phase-specific case management; • caseload 1:80; • relapse prevention; • psychoeducation.
Outcomes	Functioning (social and occupational)
Starting date	2009
Contact information	christy@lmhui.com
Notes	Funding source: Hong Kong Jockey Club Charities Trust

DATA AND ANALYSES

Comparison 1. Specialised early intervention (SEI) versus treatment as usual (TAU)

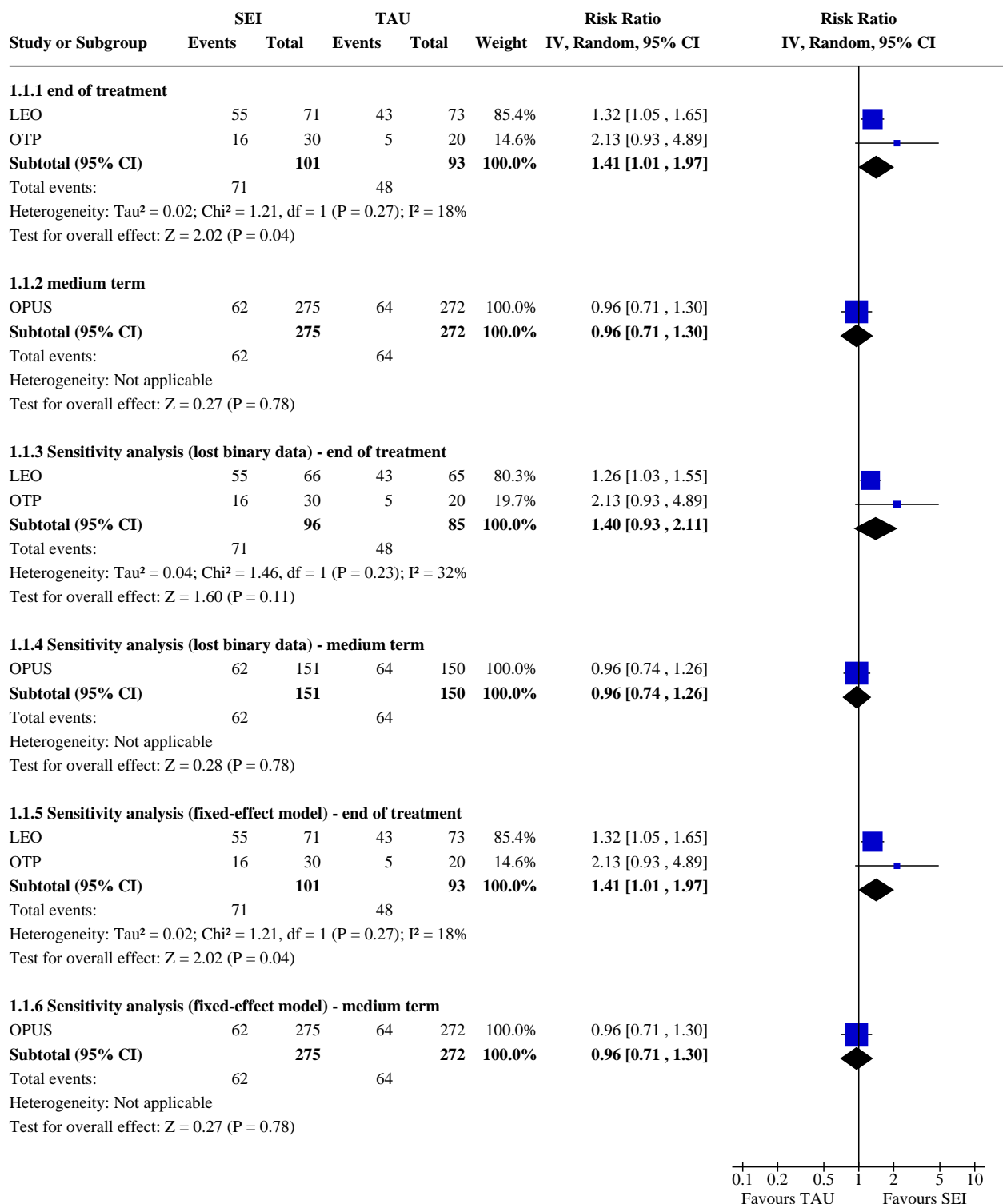
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Global state: recovery	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 end of treatment	2	194	Risk Ratio (IV, Random, 95% CI)	1.41 [1.01, 1.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.2 medium term	1	547	Risk Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.30]
1.1.3 Sensitivity analysis (lost binary data) - end of treatment	2	181	Risk Ratio (IV, Random, 95% CI)	1.40 [0.93, 2.11]
1.1.4 Sensitivity analysis (lost binary data) - medium term	1	301	Risk Ratio (IV, Random, 95% CI)	0.96 [0.74, 1.26]
1.1.5 Sensitivity analysis (fixed-effect model) - end of treatment	2	194	Risk Ratio (IV, Random, 95% CI)	1.41 [1.01, 1.97]
1.1.6 Sensitivity analysis (fixed-effect model) - medium term	1	547	Risk Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.30]
1.2 Service use: disengagement from services	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 end of treatment	3	630	Risk Ratio (IV, Random, 95% CI)	0.50 [0.31, 0.79]
1.2.2 Sensitivity analysis (lost binary data) - end of treatment	3	630	Risk Ratio (IV, Random, 95% CI)	0.50 [0.31, 0.79]
1.2.3 Sensitivity analysis (fixed-effect model) - end of treatment	3	630	Risk Ratio (IV, Random, 95% CI)	0.50 [0.31, 0.79]
1.3 Service use: admission to psychiatric hospital	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.3.1 end of treatment	4	1145	Risk Ratio (IV, Random, 95% CI)	0.91 [0.82, 1.00]
1.3.2 long term	1	50	Risk Ratio (IV, Random, 95% CI)	0.77 [0.48, 1.24]
1.4 Service use: readmission to psychiatric hospital - skewed data	2		Other data	No numeric data
1.4.1 end of treatment	1		Other data	No numeric data
1.4.2 long term	1		Other data	No numeric data
1.5 Service use: number of days in psychiatric hospital	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 end of treatment	1	547	Mean Difference (IV, Random, 95% CI)	-27.00 [-53.68, -0.32]
1.5.2 long term	1	45	Mean Difference (IV, Random, 95% CI)	-56.00 [-410.26, 298.26]
1.6 Global state: relapse	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 end of treatment	2	194	Risk Ratio (IV, Random, 95% CI)	0.71 [0.47, 1.08]
1.7 Mental state: specific, average end-point score on specific symptoms men-	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

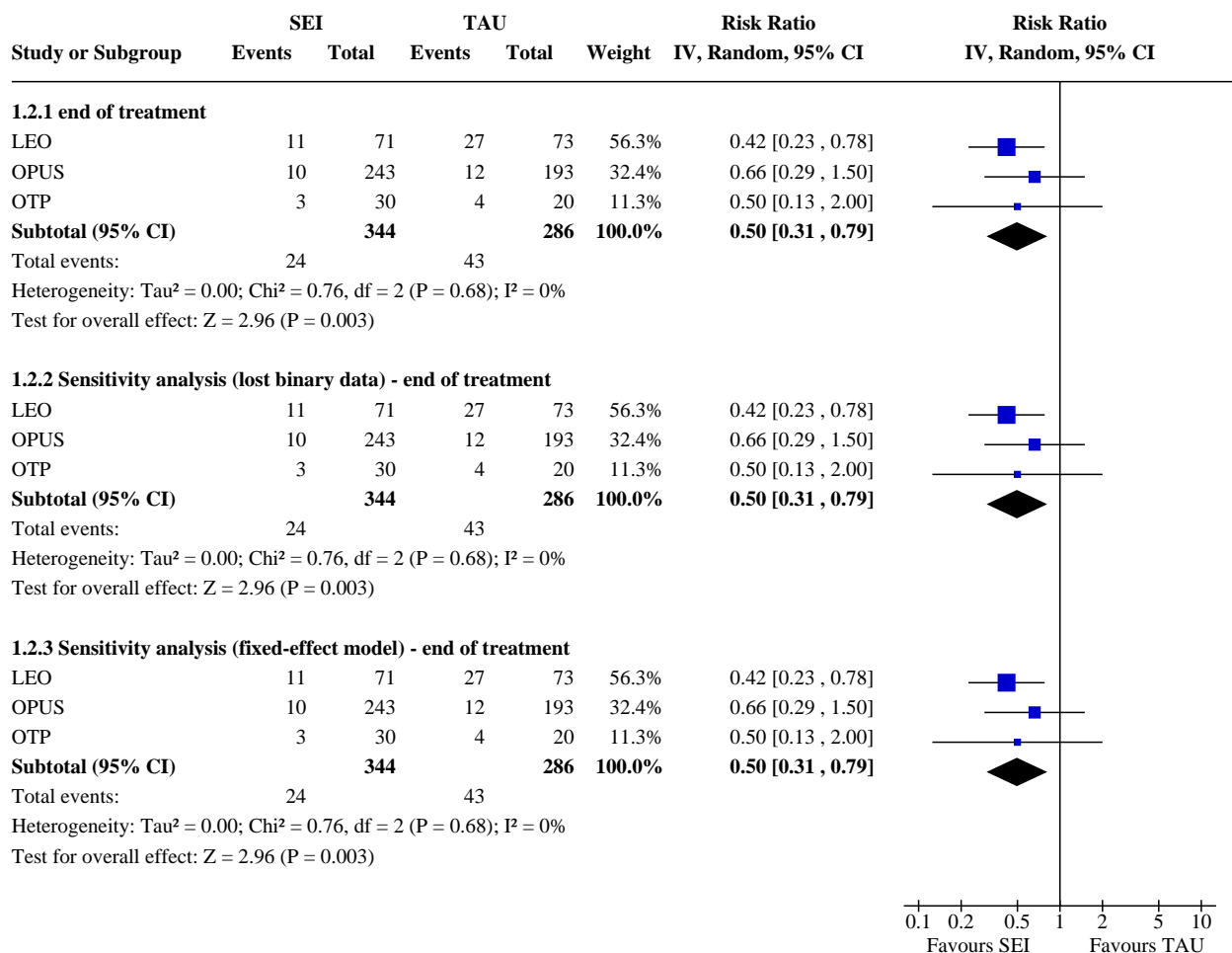
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
tal state scale/subscale, general psychotic symptoms				
1.7.1 end of treatment	2	304	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-4.58, 3.75]
1.8 Mental state: specific, average end-point score on specific symptoms mental state scale/subscale, positive psychotic symptoms	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 end of treatment	4	723	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.33, -0.03]
1.8.2 medium term	1	301	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.16, 0.29]
1.8.3 long term	1	547	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.15, 0.19]
1.9 Mental state: specific, average end-point score on specific symptoms mental state scale/subscale, negative psychotic symptoms	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 end of treatment	4	723	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.53, -0.11]
1.9.2 medium Term	1	301	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.29, 0.16]
1.9.3 long term	1	547	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.21]
1.10 Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, depressive symptoms	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 end of treatment	1	99	Mean Difference (IV, Random, 95% CI)	0.00 [-1.35, 1.35]
1.11 Behaviour: specific, occurrence of violent incidents (to self, others or property)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.11.1 end of treatment	1	547	Risk Ratio (IV, Random, 95% CI)	0.99 [0.38, 2.60]
1.11.2 medium term	1	547	Risk Ratio (IV, Random, 95% CI)	0.93 [0.47, 1.84]
1.12 Adverse effects/events: death, suicide or natural cause	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.12.1 end of treatment	3	741	Risk Ratio (IV, Random, 95% CI)	0.21 [0.04, 1.20]
1.12.2 medium term	2	691	Risk Ratio (IV, Random, 95% CI)	0.56 [0.22, 1.46]
1.12.3 long term	1	50	Risk Ratio (IV, Random, 95% CI)	0.23 [0.01, 5.28]
1.13 Leaving the study early: for any reason	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13.1 end of treatment	4	1145	Risk Ratio (IV, Random, 95% CI)	0.63 [0.54, 0.74]
1.13.2 medium term	1	547	Risk Ratio (IV, Random, 95% CI)	1.00 [0.86, 1.16]
1.14 Quality of life: recipient, overall, average endpoint score on quality of life scale	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 end of treatment	2	300	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.08, 0.60]
1.15 Functioning: general, average endpoint score on general functioning scale	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.15.1 end of treatment	2	467	Std. Mean Difference (IV, Random, 95% CI)	0.37 [0.07, 0.66]
1.15.2 medium term	1	301	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.16, 0.29]
1.15.3 long term	1	547	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.19, 0.14]
1.16 Functioning: specific, any change in education or employment status	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.16.1 end of treatment	2	951	Risk Ratio (IV, Random, 95% CI)	1.21 [0.94, 1.55]
1.17 Satisfaction with care: recipient, average endpoint score on satisfaction scale	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.17.1 end of treatment	2	463	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.51, 0.88]

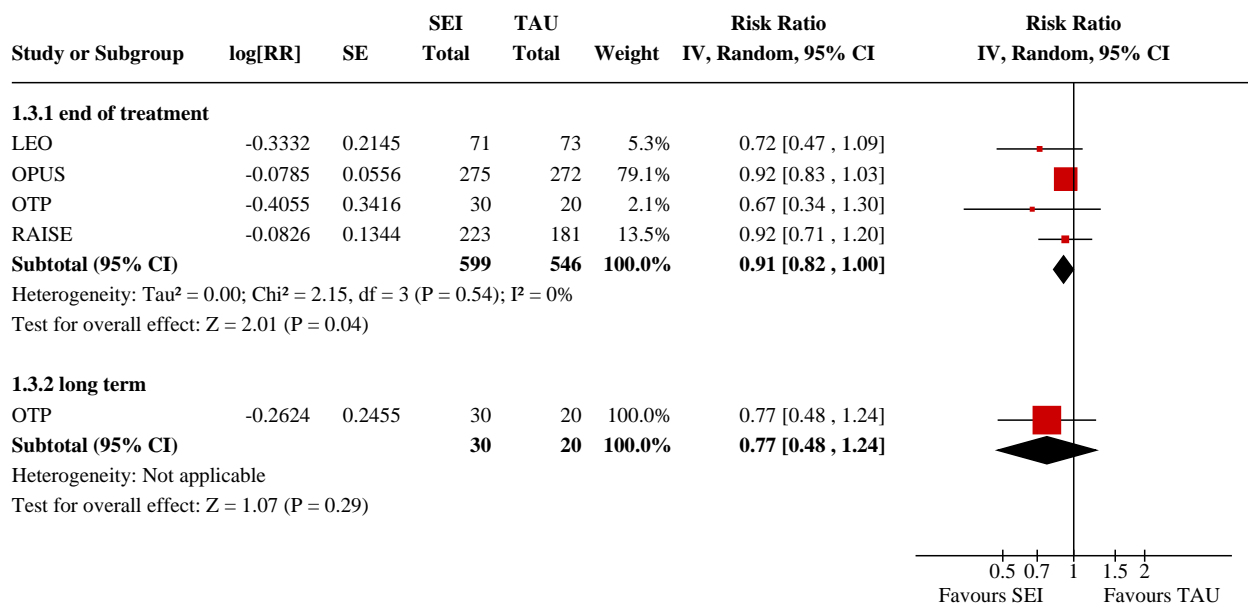
Analysis 1.1. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 1: Global state: recovery



Analysis 1.2. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 2: Service use: disengagement from services



Analysis 1.3. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 3: Service use: admission to psychiatric hospital

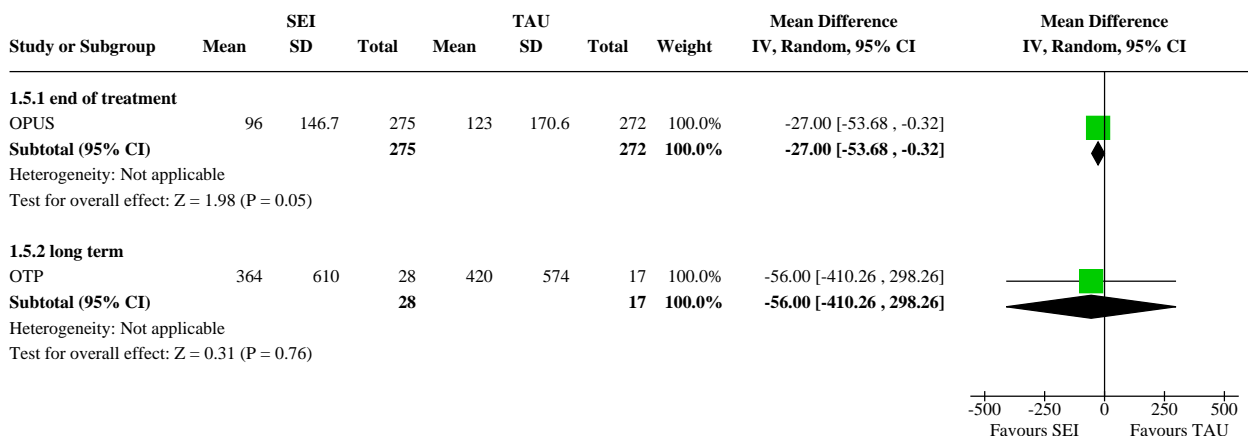


Analysis 1.4. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 4: Service use: readmission to psychiatric hospital - skewed data

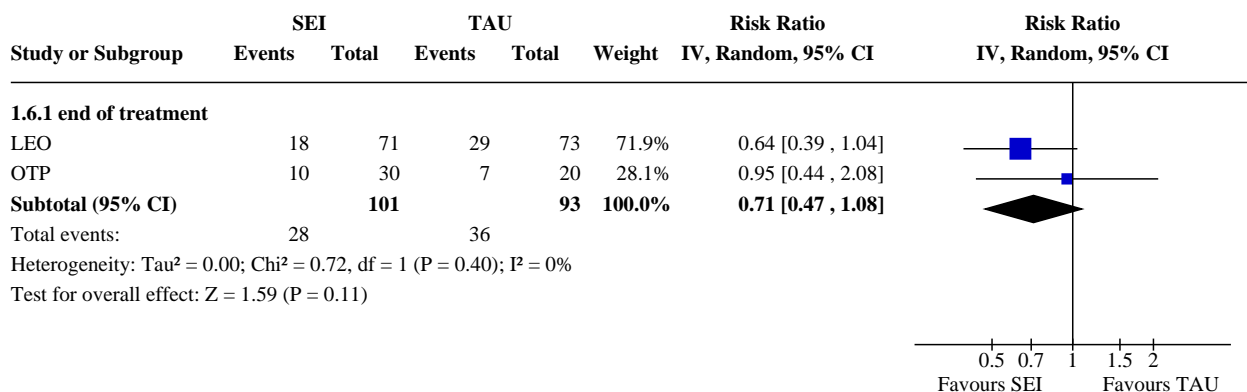
Service use: readmission to psychiatric hospital - skewed data

Study	Intervention	Mean	SD	N	Notes
end of treatment					
LEO	SEI	0.4	0.7	69	Reported a difference
	TAU	0.8	1.0	67	Reported a difference
long term					
OTP	SEI	4.4	7.9	28	Reported no difference
	TAU	6	5.7	17	Reported no difference

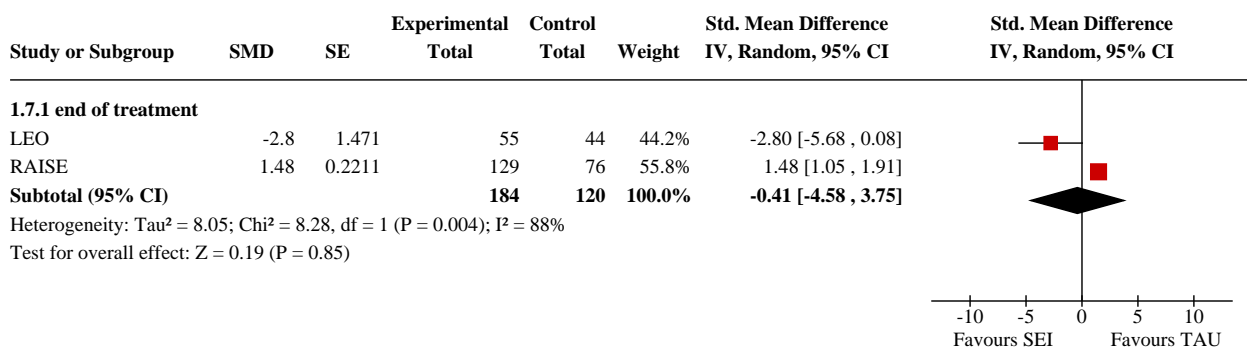
Analysis 1.5. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 5: Service use: number of days in psychiatric hospital



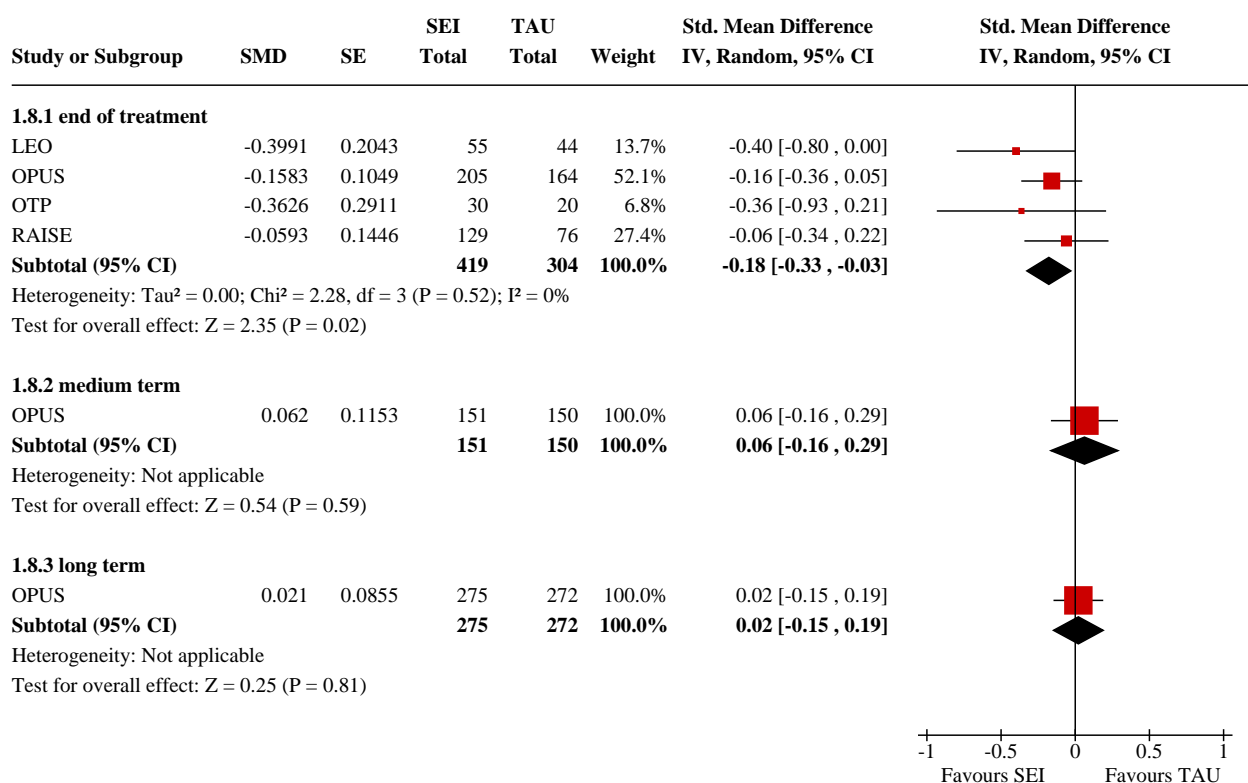
Analysis 1.6. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 6: Global state: relapse



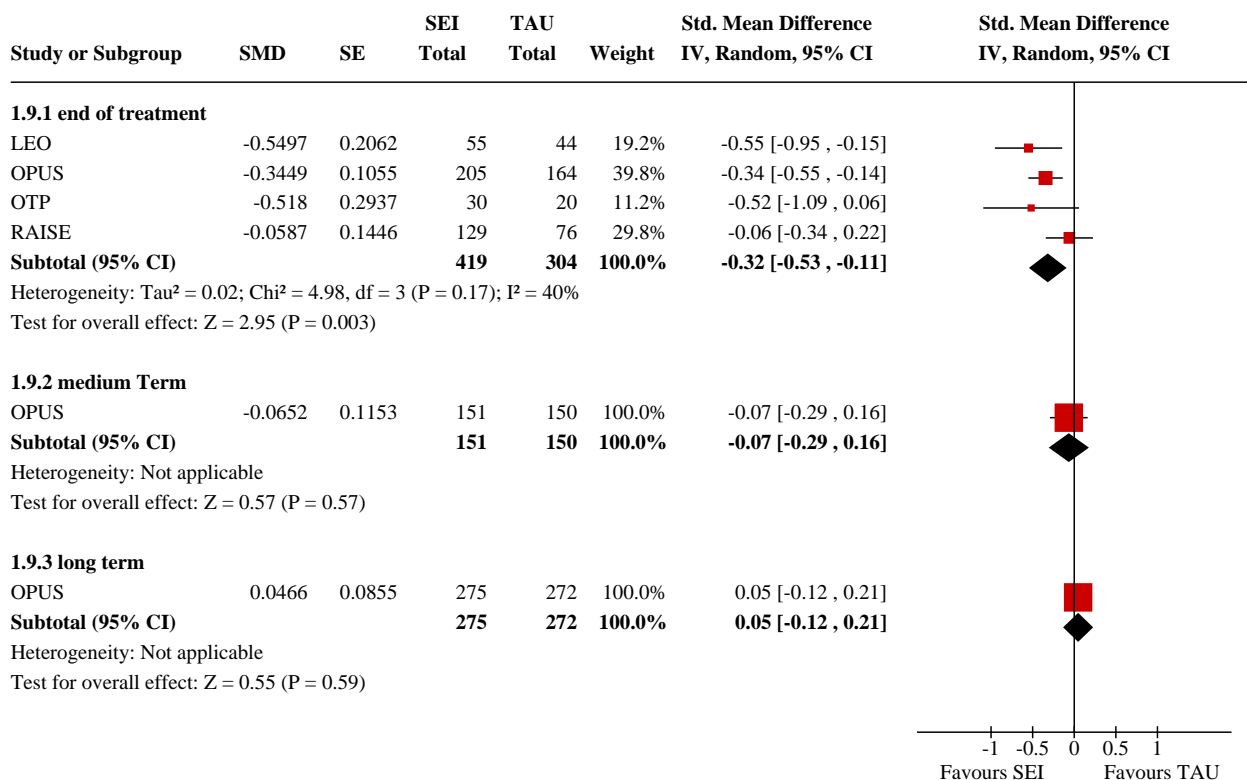
Analysis 1.7. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 7: Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, general psychotic symptoms



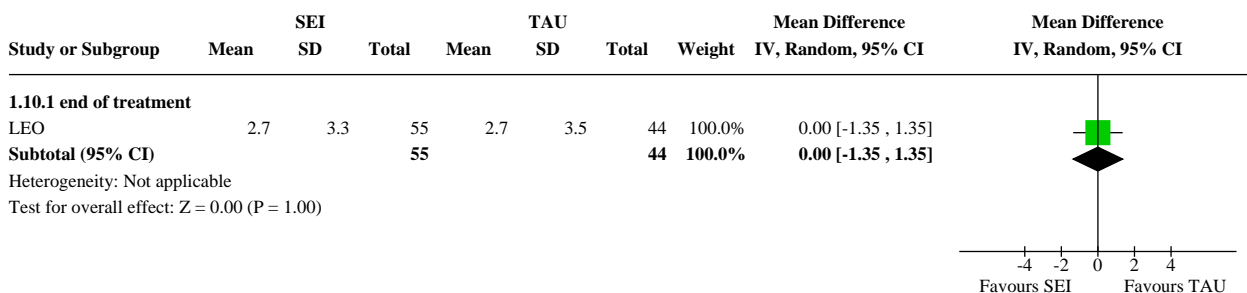
Analysis 1.8. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 8: Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, positive psychotic symptoms



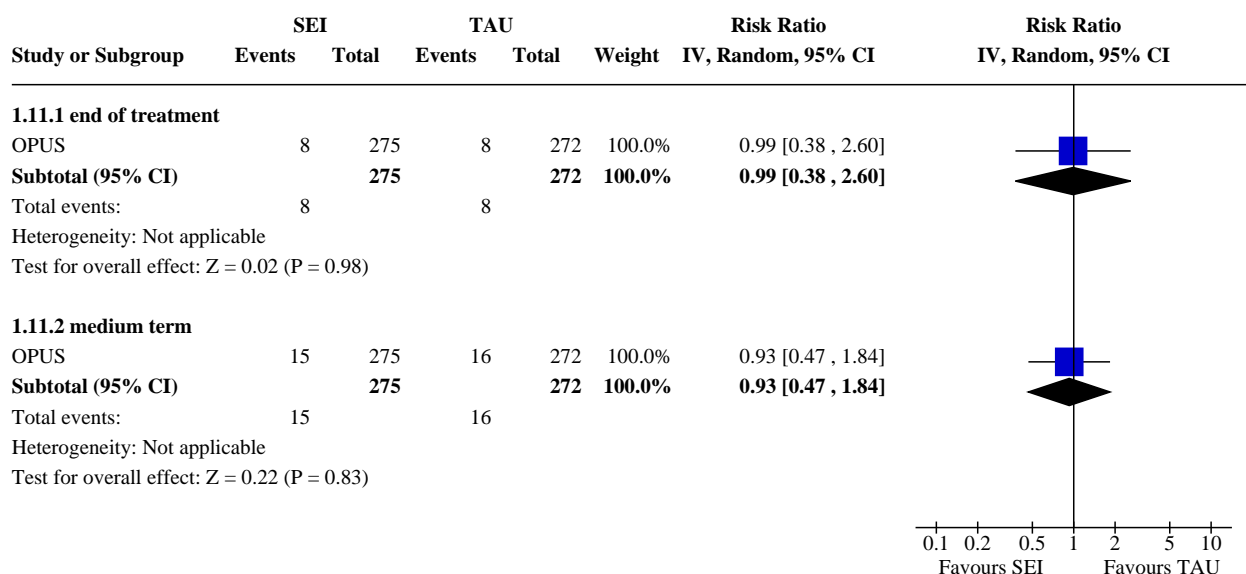
Analysis 1.9. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 9: Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, negative psychotic symptoms



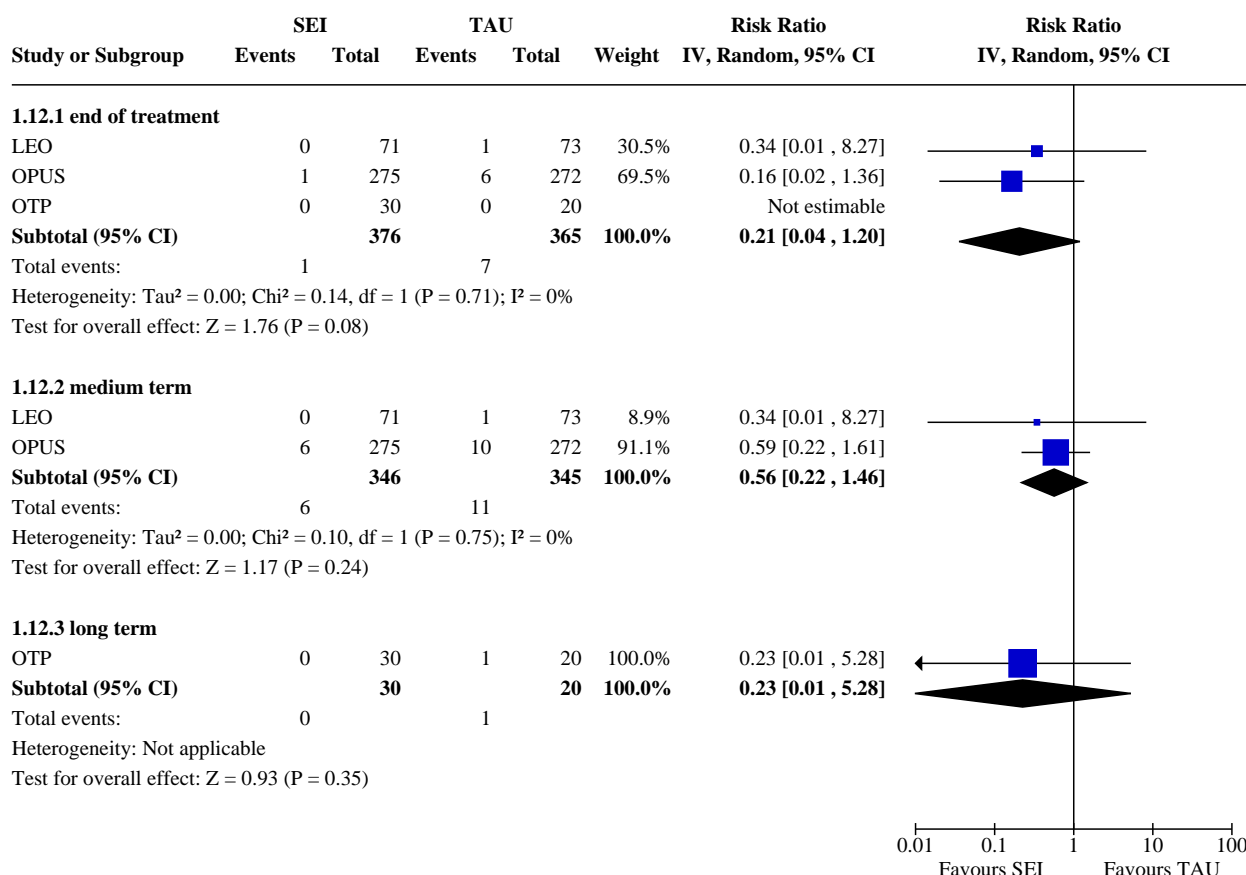
Analysis 1.10. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 10: Mental state: specific, average endpoint score on specific symptoms mental state scale/subscale, depressive symptoms



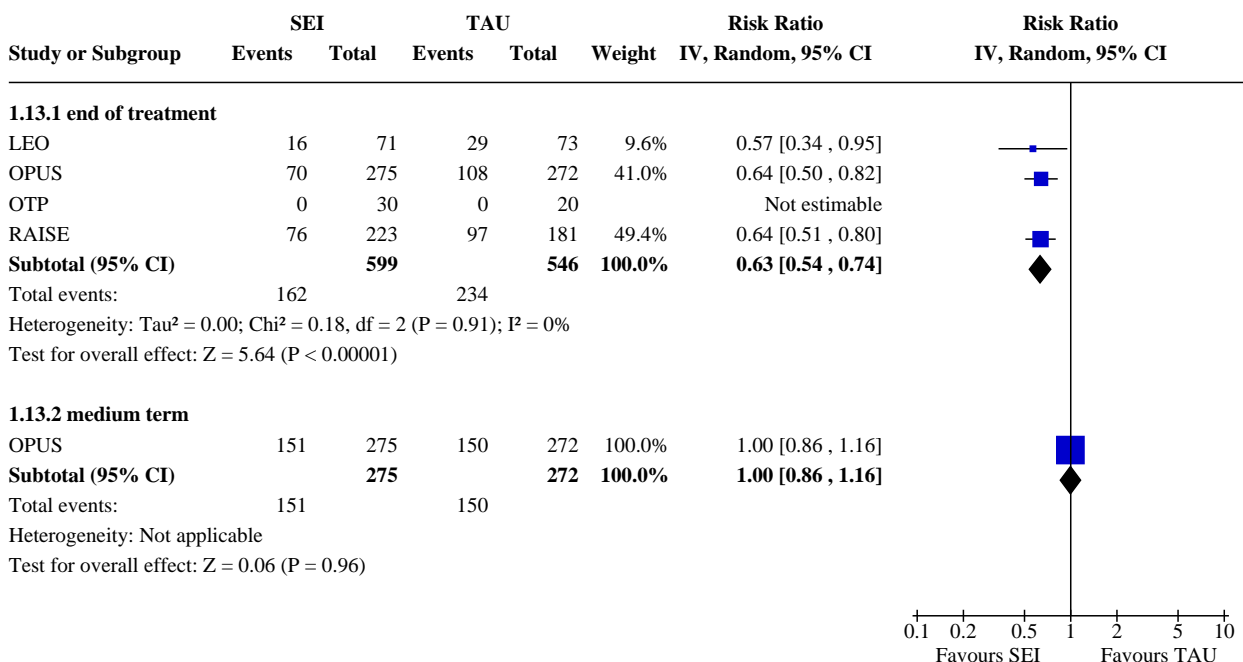
Analysis 1.11. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU), Outcome 11: Behaviour: specific, occurrence of violent incidents (to self, others or property)



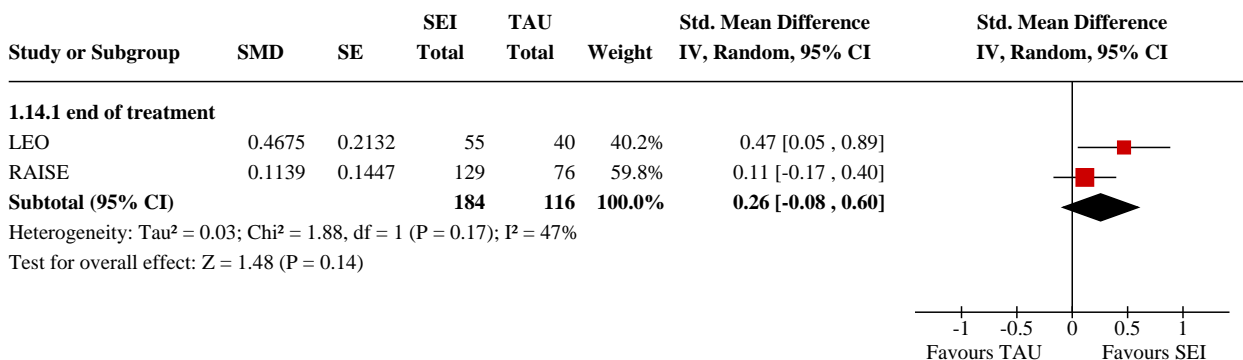
Analysis 1.12. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU), Outcome 12: Adverse effects/events: death, suicide or natural cause



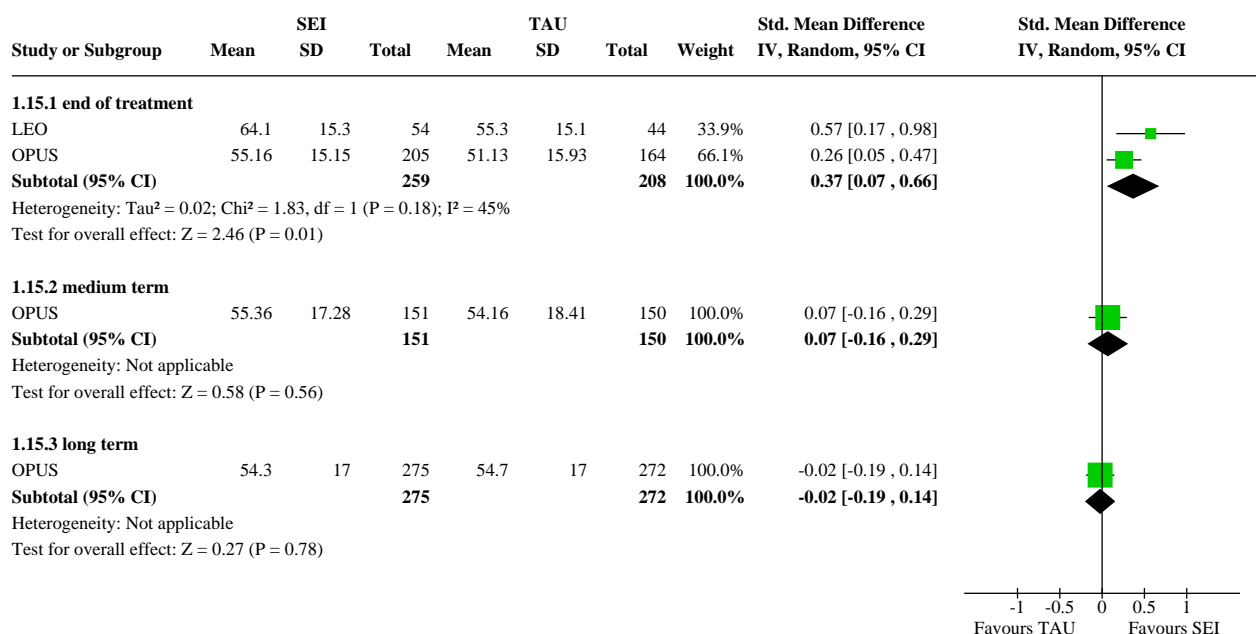
Analysis 1.13. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU), Outcome 13: Leaving the study early: for any reason



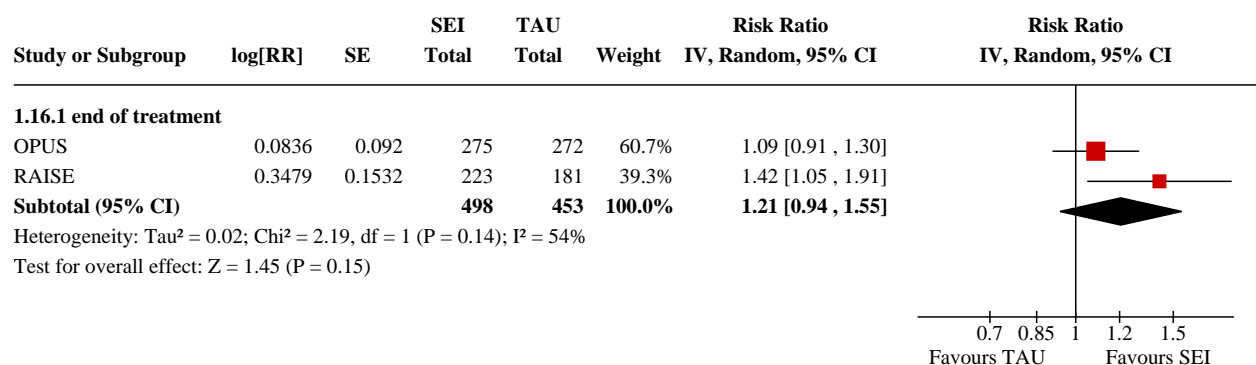
Analysis 1.14. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU), Outcome 14: Quality of life: recipient, overall, average endpoint score on quality of life scale



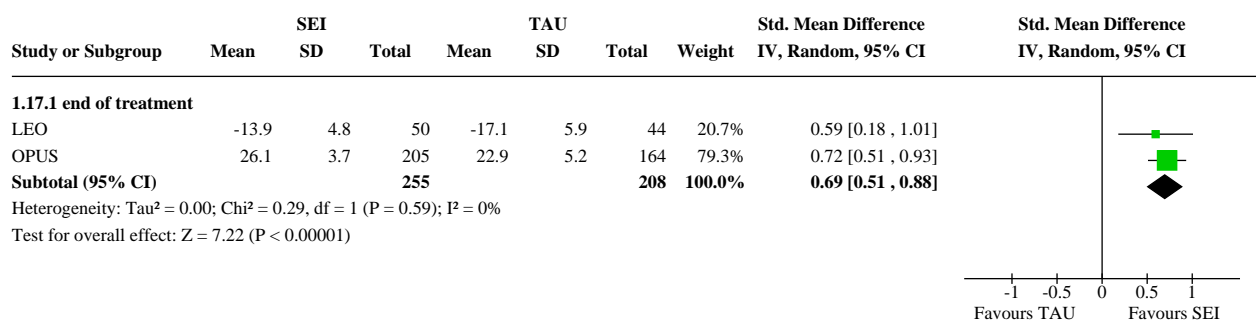
Analysis 1.15. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 15: Functioning: general, average endpoint score on general functioning scale



Analysis 1.16. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 16: Functioning: specific, any change in education or employment status



Analysis 1.17. Comparison 1: Specialised early intervention (SEI) versus treatment as usual (TAU, Outcome 17: Satisfaction with care: recipient, average endpoint score on satisfaction scale



ADDITIONAL TABLES

Table 1. Suggested future study design

Methods	Allocation: randomised Blinding: n/a. There is a very low likelihood of blinding being maintained in a such a complex intervention. Duration: two or three years intervention period, at least > 1-year follow-up period
Participants	Diagnosis: psychosis and related diagnoses N = 440* Gender: men and women Age: 14 - 65
Interventions	SEI comprised of recommended set of interventions: assertive community contact, small caseload size, offer of cognitive behaviour therapy for psychosis, family intervention, individual placement and support.
Outcomes	Global state: recovery** Global state: relapse Service use: disengagement from services Service use: admission to psychiatric hospital Functioning: clinically important change in functioning Quality of life: clinically important change in quality of life Economics: cost of care
Notes	* Sample size suggested relates to the size of a study with sufficient power to highlight a 10% difference between groups for the primary outcome if recovery in the intervention arm is 35% ** Primary outcome

HISTORY

Protocol first published: Issue 3, 2019

Review first published: Issue 11, 2020

CONTRIBUTIONS OF AUTHORS

Stephen Puntis: development and writing of the review, study selection, statistical analysis

Amedeo Minichino: development and writing of the review, study selection, statistical analysis

Franco De Crescenzo: development and writing of the review, study selection, statistical analysis

Rachael Harrison: study selection, writing of the review

Andrea Cipriani: development and writing of the review, advised with study selection and statistical analysis

Belinda Lennox: development and writing of the review, advised with study selection and statistical analysis

DECLARATIONS OF INTEREST

Stephen Puntis: SP currently receives research grants for the purpose of investigating the effectiveness of early intervention in psychosis services

Amedeo Minichino: AM currently receives Medical Research Council funding for a DPhil studentship

Franco De Crescenzo: none

Rachael Harrison: none

Andrea Cipriani: Andrea Cipriani has received research grants and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work.

Belinda Lennox: I work clinically in an early intervention in psychosis service, and am clinical lead for early intervention in psychosis for NHS England. I am an investigator on a pending NIHR HTA award examining extended early intervention services. I have received travel expenses from Lundbeck and Alkermes, fees for consultancy work for Astellas, and share income from GlaxoSmithKline, all outside the submitted work. No other declarations of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol the title of the review was 'Specialised early intervention teams for first episode psychosis'; in the review we changed the title to: 'Specialised early intervention teams for recent-onset psychosis.' We have explained our decision to use the term 'recent-onset psychosis' rather than 'first episode psychosis' in the [Description of the condition](#).

In the protocol we used the following intervention term: 'early intervention in psychosis' (EIP); in the review we changed this to: 'specialised early intervention' (SEI).

In the protocol we used the following terms for the comparator: 'usual community mental health care' or 'standard care' or 'treatment as usual'; in the review we standardised this to 'treatment as usual' (TAU).

Timing of outcome assessment: in the protocol, we categorised timing of outcome assessments into short term (up to 12 months post-treatment), medium term (13 to 60 months post-treatment), and long term (longer than 60 months post-treatment). In the review we have grouped these outcome assessments into end of treatment, medium term (1 to 60 months post treatment) and long term (longer than 60 months post-treatment).

We have included relapse as an outcome in the full review. Relapse was measured as the proportion of participants who had relapsed, as defined by the study. We did not include relapse as an outcome in our protocol due to researcher error after a version edit of the protocol. We have added relapse to [Types of outcome measures](#), [Effects of interventions](#) and [Data and analyses](#) sections.

We have used standardised mean difference (SMD) where different scales which assessed the same construct were comparable, while we have used mean difference (MD) where the construct was measured with the same scale. In our protocol we aimed to only use MD.