Supplementary Online Content

Correll CU, Galling B, Pawar A, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry*. Published online May 2, 2018. doi:10.1001/jamapsychiatry.2018.0623

References

This supplementary material has been provided by the authors to give readers additional information about their work.

sOnline-Only Supplement Material

Supplement 1: eMethods 1. **Study Protocol**

Effectiveness of Coordinated Specialty Care for Early Psychosis: Systematic Review, Meta-analysis, and Meta-regression-Analysis

Start date: 02/06/2015

Anticipated completion date: 09/30/2016

Review Question (s)

Is coordinated specialty care (EIS) superior to usual care/modular care (UC/MC) for individuals with early psychosis?

Searches

Databases:

The following databases will be searched to identify randomized controlled trials comparing interventions consisting of coordinated specialized care (EIS) and usual care/modular care (UC/MC).

EMBASE (Ovid) (1947-present)

Ovid MEDLINE ® In-Process and Other Non-Indexed Citations and Ovid MEDLINE ® (1946-Present)

Ovid PsycINFO (1806- Present)

PubMed (NLM) (1946-Present)

Clinicaltrials.gov

Search Terms:

In order to identify relevant studies, our search strategies will use a combination of subject headings, and free text search terms including the following terms:

(schizophrenia OR schizoaffective OR schizophreniform OR psychosis OR psychotic) AND (recent-onset OR "recent onset" OR "first episode" OR first-episode OR "early psychosis") AND (intervention OR integrat* OR multimodal OR assertive OR specialized OR "OPUS" OR "OTP" OR "LEO" OR "COAST" OR "STEP" OR "RAISE")

The final strategies will include relevant synonyms and incorporate appropriate search tools to ensure maximum sensitivity.

The search strategy was developed by the review team. It was adapted from a published systematic review on early intervention services, cognitive-behavioural therapy and family intervention in early psychosis [1].

Two independent authors will conduct the systematic literature search separately. There are no restrictions to publication period or language.

Types of study to be included

Randomized controlled trials (RCTs) comparing an intervention consisting of coordinated specialized care (EIS), i.e., an integrated/multimodal program for study-defined diagnosis of first-episode psychosis or early-phase schizophrenia-spectrum disorder and a control group consisting of a non-specialized usual care/modular care (UC/MC).

Exclusion of RCTs randomizing patients to maintenance of EIS versus a step-down/less intense maintenance treatment.

Condition or Domain to be studied

Outcomes in schizophrenia-spectrum disorders have remained suboptimal. Schizophrenia is among the ten most debilitating disorders in the US [2], being associated with the highest disability weights [3], and resulting in enormous personal and societal cost.

A recent meta-analysis suggested that over the last five decades the rate of recovery was low (median=13.5%) and has not improved significantly over time [4]. Furthermore, people with schizophrenia die on average 15-20 years prematurely [5], with an increasing mortality gap [6]. Issues negatively affecting symptomatic, functional, and quality of life outcomes include insufficient engagement in/response to often fragmented usual care options, and insufficient provision of/ evidence-based treatments, particularly, integrated multimodal treatment.

Since people with early-phase schizophrenia generally respond better to treatment and have not yet endured many years of illness effects and functional decline, there has been an increasing focus on the early identification and optimized management of people in the early illness phases. Several large, federally funded treatment programs have been launched for early-phase schizophrenia-spectrum patients that yielded promising results for coordinated specialty care (EIS) [7–9]. These programs aimed particularly at not only symptom reduction, but also focused on improving functional outcomes, and reducing long-term disability during what has been called a "critical illness period" [10].

So far, only one meta-analysis has summarized the main effects of randomized studies that compared EIS versus usual care/modular care (UC/MC), consisting of a more restricted array of modular, non-coordinated treatment modalities that were not adapted to the needs of early-phase patients [1]. In that meta-analysis the efficacy of four studies was assessed for seven outcomes, reported by only 2-3 studies, except for all-cause discontinuation (studies=4). Results indicated superiority of EIS in early-phase schizophrenia patients. In addition to the restricted number of studies, patients, and outcomes in that meta-analysis, only published data were included, no subgroup- or meta-regression analyses were conducted, and neither different treatment elements nor the time course of the treatment effects were examined. Moreover, the degree to which treatment gains could be sustained after discontinuing EIS was not examined.

Because many additional randomized studies of EIS vs UC/MC were published since, we will conduct a comprehensive meta-analysis of all available studies, including all available data, aiming also to report data not reported in the publications. We hypothesize that EIS will be superior to UC/MC.

Participants

Inclusion criteria:

i) Adolescents and adults aged >/=12 years old
ii) Study-defined diagnosis of first-episode psychosis or early-phase schizophrenia-spectrum disorder (schizophrenia, psychotic disorder not otherwise specified (NOS), schizoaffective disorder, schizophreniform disorder, delusional disorder)
iii) Randomized to an intervention consisting of coordinated specialized care (EIS) for early psychosis or a control group consisting of a non-specialized usual care/modular care (UC/MC)

Intervention(s), Exposure(s)

This review will include any treatment consisting of coordinated specialized care (EIS), i.e., an integrated / multimodal treatment program for individuals with early psychosis

Comparator(s)/Control

Study-defined usual care/modular care (UC/MC) for individuals with early psychosis

Context

N/A

Primary Outcome

We will use the following co-primary outcomes:

- All-cause treatment discontinuation
- >/=1 psychiatric hospitalization

Secondary Outcome(s)

We use the following key secondary outcomes:

- Total symptom improvement [measured with a validated scale, e.g., Positive and Negative Syndrome Scale (PANSS)[11] or Brief Psychiatric Rating Scale (BPRS)[12]]
- Functioning [measured with a validated scale, e.g., Global Assessment of Functioning scale (GAF)[13]]
- Work or school involvement

Other outcomes:

- Symptom severity (positive, negative, general, and depressive symptoms) [measured with a validated scale, e.g., Positive and Negative Syndrome Scale (PANSS) subscales [11], Brief Psychiatric Rating Scale (BPRS) subscales [12], Scale for the Assessment of Positive Symptoms (SAPS)[14], Scale for the Assessment of Negative Symptoms (SANS)[15], Hamilton Rating Scale for Depression (HAM-D)[16]]
- Remission (study-defined, defined as symptom stability and/or minimum symptom severity)
- Recovery (study-defined, defined as symptom stability/minimum severity plus improved social, educational or vocational attainment),
- Relapse
- Duration of hospitalization

- Quality of life

Data Extraction (selecting and coding)

Study selection:

Citations and available abstracts of the search results will be uploaded in Zotero and screened for potential eligibility. This will be done in two stages. The first stage will involve screening the titles and abstracts to exclude studies not meeting the inclusion criteria. At least two reviewers will independently screen all citations. Discrepancies will be resolved through consensus and where an agreement cannot be reached, a third reviewer will be involved.

In the second stage, at least two reviewers will independently screen the full text of the remaining studies and assess them for eligibility. Any missing data that could help assess eligibility will be sought by contacting the corresponding authors. For studies that are excluded during this stage, a reason for exclusion will be recorded for later reporting. Any discrepancies at this stage will be resolved through consulting a third reviewer who will independently assess the study under consideration. For included studies, multiple reports from the same study will be linked. For overlapping samples, the largest sample with data will be included.

Data extraction:
Data will be extracted using a pre-piloted data extraction template. Information will be extracted on the following general information:

- Study reference
- Number of patients randomized
- Number of patients analyzed
- Number of sites
- Country
- Setting at Recruitment (Outpatients, Inpatients, Inpatients and Outpatients)
- Blinded outcome assessments (yes, no)
- Fidelity monitoring (yes, no)
- Trial duration
- Data used (intent-to-treat vs observed cases)
- Primary Outcome
- Secondary Outcome
- Timepoints assessments (baseline, 6 months, 9 months, 12 months, 18 months, 24 months)
- Drop-out rate at each time point (baseline, 6 months, 9 months, 12 months, 18 months, 24 months)
- Risk of bias (Selection bias, allocation bias, performance bias, detection bias, attrition bias, reporting bias, other bias) and number of low risk ratings
- Treatment components (medication review, vocational/ educational support, CBT, family psychoeducation, family therapy, crisis response team, social skills training) and total number of components
- Mean number of visits in each treatment group and ratio between intervention groups
- Psychiatric diagnoses of participants (n, %)
- Duration of mental illness
- Mean duration of previous treatment
- Mean GAF at baseline
- Mean PANSS/BPRS at baseline

- Mean PANSS-POS at baseline
- Mean PANSS-NEG at baseline
- Number of prior hospitalizations
- Mean age of participants
- Gender distribution
- Mean duration of untreated psychosis
- Median duration of untreated psychosis

Additionally, information on all outcomes (see above) will be abstracted.

Risk of bias (quality) assessment

Each included study will be assessed using the Cochrane Risk of Bias (ROB) tool - a validated tool designed to assess the quality of randomised trials. The number of low risk judgements will be counted for each study. The more low-risk judgements a study is awarded, the higher the quality of the study. A maximum of 7 low-risk judgements can be given. Two reviewers will independently assess study quality and generate a ROB score. Discrepancies will be resolved through consensus, and a third reviewer will be consulted to resolve any remaining disagreement.

Strategy for Data Synthesis

We plan to conduct a random effects[17] meta-analysis of outcomes for which ≥2 studies contribute data, using Comprehensive Meta-Analysis V3 (http://www.meta-analysis.com).

In the primary analyses, EIS and UC/MC will be compared at study endpoint. Intent-to-treat (ITT) data will be used whenever possible. Continuous outcomes will be expressed as the standardized mean difference (SMD) preferring change scores (unless skewed, i.e., SD >twice the mean) over time point/endpoint scores, while categorical data will be expressed as the pooled Mantel-Haenszel relative risk (RR), each with their 95% confidence intervals (CIs). For categorical outcomes, numbers-needed-to-treat (NNTs) will be calculated dividing the absolute risk difference by 1. We will explore study heterogeneity using the chi-square test of homogeneity and I^2 statistics, with $p<0.05$ and I^2 >50%, respectively, indicating significant heterogeneity. All analyses were two-tailed with alpha=0.05.

Demographic information about the pooled study samples will be calculated by weighting the study mean values according to sample size.

Publication bias will be assessed by visually inspecting funnel plots. In addition, we will when appropriate calculate the Egger bias test (11). Then, to account for publication bias, we will use the trim-and-fill method, based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished studies (11). Finally, the fail-safe number of negative studies that would be required to nullify (i.e. make $p > 0.05$) the ES will also be calculated.

In secondary analyses, outcomes were analyzed by specific time period, i.e., early (6 months), medium-term (9-12 months) and longer-term (18-24 months). Additionally, the maintenance effect of the intervention was analyzed using data of the follow up-phase.

Analysis of subgroups or subsets

We will explore subgroups as follows:

i) analyzed data type (ITT vs OC)
ii) region (Europe vs USA vs Rest of the world)
iii) blinding of outcome assessments
iv) fidelity monitoring
v) use of family therapy,
vi) use of crisis response teams
vii) use of social skills training
viii) use of vocational/educational rehabilitation.

Where data allow we will conduct exploratory maximum likelihood random effects meta-regression analyses of the co-primary outcomes and the three key secondary outcomes to identify potential moderators or mediators, including:

ix) sample size
x) number of sites
xi) study quality (Cochrane risk of bias tool)
xii) intervention characteristics (duration, number of EIS treatment components, ratio of visits)
xiii) patient characteristics (mean age, percentage males)
xiv) illness characteristics (percentage with schizophrenia, illness duration, duration of untreated psychosis (DUP), duration of antipsychotic treatment prior to baseline, number of prior hospitalizations)
xv) symptom severity and functioning at baseline (GAF, PANSS, PANSS-converted BPRS, PANSS-Positive, PANSS-Negative).

Type and method of review

Meta-analysis

Language

English

Country

United States of America, Canada, Demark, Germany, Hong Kong, Italy, Netherlands, Mexico, United Kingdom

Dissemination Plans

The results of the review will be disseminated locally, nationally and internationally through the following channels:

1. A paper will be submitted to a leading peer-reviewed journal in this field, and conference presentations will be given.
2. Findings will be disseminated to healthcare professionals and commissioners involved in mental health care through professional journals and magazines, conferences and meetings.

Keywords

Early Psychosis, First Episode, Coordinated Specialty Care, Comprehensive Care, Integrated Care, Meta-analysis

Details of any existing review of the same topic by the same authors

None

Contact details for further information

Christoph U. Correll, M.D.

The Zucker Hillside Hospital
Psychiatry Research
75-59 263rd Street
Glen Oaks, NY 11004
Tel: 718 4704812
Fax: 718 3431659
Email address: ccorrell@nshs.edu

Review Team

Christoph U. Correll, MD
Britta Galling, MD
Aditya Pawar, MD
Anastasia Krivko, MD
John M. Kane, MD

Organisational affiliation of the review

The Zucker Hillside Hospital
Psychiatry Research
75-59 263rd Street
Glen Oaks, NY 11004

Collaborators

As above

Funding sources/sponsors

No funding has been received for this review.

Conflicts of interest

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, Medavante, Medscape, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck and Pfizer. He received grant support from

Takeda. Dr. Kane has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forum, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medscape, Merck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Pfizer, Reviva, Roche, Sunovion, Takeda and Teva. He is a shareholder of MeAvante, LB Pharma and The Vanguard Research Group.

Any other information

None

References

1. Bird V, Premkumar P, Kendall T, Whittington C, Mitchell J, Kuipers E. Early intervention services, cognitive-behavioural therapy and family intervention in early psychosis: systematic review. *Br J Psychiatry*. 2010;197(5):350-356. doi:10.1192/bjp.bp.109.074526.

2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet Lond Engl*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2.

3. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet Lond Engl*. 2012;380(9859):2129-2143. doi:10.1016/S0140-6736(12)61680-8.

4. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;39(6):1296-1306. doi:10.1093/schbul/sbs130.

5. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.

6. Nielsen RE, Uggerby AS, Jensen SOW, McGrath JJ. Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades--a Danish nationwide study from 1980 to 2010. *Schizophr Res*. 2013;146(1-3):22-27. doi:10.1016/j.schres.2013.02.025.

7. Birchwood M, Lester H, McCarthy L, et al. The UK national evaluation of the development and impact of Early Intervention Services (the National EDEN studies): study rationale, design and baseline characteristics. *Early Interv Psychiatry*. 2014;8(1):59-67. doi:10.1111/eip.12007.

8. Verma S, Poon LY, Subramaniam M, Abdin E, Chong SA. The Singapore Early Psychosis Intervention Programme (EPIP): A programme evaluation. *Asian J Psychiatry*. 2012;5(1):63-67. doi:10.1016/j.ajp.2012.02.001.

9. Jørgensen P, Nordentoft M, Abel MB, Gouliaev G, Jeppesen P, Kassow P. Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of the trial. *Soc Psychiatry Psychiatr Epidemiol*. 2000;35(7):283-287.

10. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl*. 1998;172(33):53-59.

11. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

12. Ventura J, Lukoff KH, Nuechterlein KH, Liberman RP, Green MF, Shaner A. Manual for the Expanded Brief Psychiatric Rating Scale. *Int J Methods Psychiatr Res*. 1993;3:227-244.

13. Hall RCW. Global Assessment of Functioning: A Modified Scale. *Psychosomatics*. 1995;36(3):267-275. doi:10.1016/S0033-3182(95)71666-8.

14. Andreasen NC. The Scale for the Assessment of Positive Symptoms (SAPS). *Universtiy Iowa*. 1984.

15. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS). *Univ Iowa*. 1984.

16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

18. Kuipers E, Holloway F, Rabe-Hesketh S, Tennakoon L. An RCT of early intervention in psychosis: Croydon Outreach and Assertive Support Team (COAST). *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(5):358-363. doi:10.1007/s00127-004-0754-4.

19. Hui CLM, Chang WC, Chan SKW, et al. Early intervention and evaluation for adult-onset psychosis: the JCEP study rationale and design. *Early Interv Psychiatry*. 2014;8(3):261-268. doi:10.1111/eip.12034.

20. Craig TKJ. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*. 2004;329(7474):1067-0. doi:10.1136/bmj.38246.594873.7C.

21. Petersen L. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331(7517):602-0. doi:10.1136/bmj.38565.415000.E01.

22. Grawe RW, Falloon IRH, Widen JH, Skogvoll E. Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatr Scand*. 2006;114(5):328-336. doi:10.1111/j.1600-0447.2006.00799.x.

23. Ruggeri M, Bonetto C, Lasalvia A, et al. Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants. *Schizophr Bull*. May 2015. doi:10.1093/schbul/sbv058.

24. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. *Am J Psychiatry*. October 2015:appiajp201515050632. doi:10.1176/appi.ajp.2015.15050632.

25. Srihari VH, Tek C, Kucukgoncu S, et al. First-Episode Services for Psychotic Disorders in the US Public Sector: A Pragmatic Randomized Controlled Trial. *Psychiatr Serv*. 2015. http://ps.psychiatryonline.org/doi/10.1176/appi.ps.201400236. Accessed May 14, 2015.

26. Valencia M, Juarez F, Ortega H. Integrated Treatment to Achieve Functional Recovery for First-Episode Psychosis. *Schizophr Res Treat*. 2012;2012:e962371. doi:10.1155/2012/962371.

27. Valencia M, Juarez F, Delgado M, Díaz A. Early Intervention to Improve Clinical and Function-al Outcome in Patients with First Episode-Psychosis. In: *Mental Disorder*. Vol Hong Kong: iConcept Press; 2014.

Supplement 2: eMethods 2. **Search terms**

Search terms: (schizophrenia OR schizoaffective OR schizophreniform OR psychosis OR psychotic) AND (recent-onset OR “recent onset” OR “first episode” OR first-episode OR “early psychosis”) AND (intervention OR integrat* OR multimodal OR assertive OR specialized OR “OPUS” OR “OTP” OR “LEO” OR “COAST” OR “STEP" OR “RAISE”).

Supplement 3: eMethods 3. **Overview Outcome Definitions and Scales**

Outcome	**Definition/ Scale Used**
All-cause treatment discontinuation	Percentage of patients who dropped out of the study and treatment for any potential reason, including inefficacy-related treatment discontinuation, adverse effect-related discontinuation.
≥1 psychiatric hospitalization	Percentage of patients with ≥1 psychiatric hospitalization. All psychiatric re-hospitalizations for any reason and independent of length of hospitalization were counted while potential initial hospitalization before the initiation of the EIS intervention were not included.
Total symptom improvement	Positive and Negative Syndrome Scale (PANSS)
	Brief Psychiatric Rating Scale (BPRS)
Global Functioning	Global Assessment of Functioning scale (GAF)
Work and school involvement	Percentage of patients with study-defined work and school involvement
Positive, negative, and general symptoms	PANSS and BPRS subscales
	Scale for the Assessment of Positive Symptoms (SAPS)
	Scale for the Assessment of Negative Symptoms (SANS)
Depression	Hamilton Rating Scale for Depression (HAM-D)
	Calgary Depression Scale for Schizophrenia (CDSS)
Remission	Percentage of patients who met the study-defined definition of remission, indicating symptom stability and/or minimum symptom severity
Recovery	Percentage of patients who met the study-defined definition of remission, indicating symptom stability/minimum severity plus improved social/ educational/ vocational attainment
Relapse	Percentage of patients who met the study-defined definition of relapse
Mean number of hospitalizations	Mean number of psychiatric re-hospitalizations per patient for any reason and independent of length of hospitalization excluding potential initial hospitalization before the initiation of the EIS intervention
Mean bed days	Mean number of psychiatric bed days per patient for any reason excluding potential initial hospitalization before the initiation of the EIS intervention
Quality of Life	Heinrich's Quality of Life Scale (QLS)
	SF-12

Supplement 4: eMethods 4. **Subgroup and meta-regression analyses**

Subgroup analyses included: i) analyzed data type (ITT *vs* OC), ii) region (Europe *vs* USA *vs* Rest of the world (ROTW)), iii) blinding of outcome assessments, iv) fidelity monitoring, and the use of any of the following treatment-components in EIS: v) family therapy, vi) crisis response teams, vii) social skills training, and viii) vocational/educational rehabilitation. Meta-regression variables included: i) sample size, ii) number of sites, iii) study quality (Cochrane risk of bias tool), iv) intervention characteristics (duration, number of EIS treatment components, ratio of visits EIS versus UC/MC), v) patient characteristics (mean age, percentage male), vi) illness characteristics (percentage with schizophrenia, illness duration, duration of untreated psychosis (DUP), duration of antipsychotic treatment prior to baseline, number of prior hospitalizations), and vii) symptom severity and functioning at baseline (GAF, PANSS, PANSS-converted BPRS, PANSS-Positive, PANSS-Negative).

In secondary analyses, outcomes were analyzed by specific time period, i.e., early (6 months), medium-term (9-12 months) and longer-term (18-24 months). Additionally, the maintenance effect of the intervention was analyzed using data of the follow up-phase.

Supplement 5: eMethods 5. **Post-hoc sensitivity analyses**

Outcome	**Definition**
Overall attrition rate	% of drop-outs from baseline till study endpoint
Between-group attrition difference*	Calculated by subtracting the EIS attrition rate from the TAU attrition rate.
*In one study the between-group attrition difference was <0 (-1.1). To enable inclusion of this study to meta-regression analyses, 10 percent were added to the raw between-group attrition difference, as this does not influence the outcomes.	

Supplement 6: eTable 1. **Included studies and papers**

Study (Number of papers)	Reference	Acute	Maintenance
COAST (1)[1]	**Kuipers, E., Holloway, F., Rabe-Hesketh, S., & Tennakoon, L. (2004). An RCT of early intervention in psychosis: Croydon Outreach and Assertive Support Team (COAST). *Social Psychiatry and Psychiatric Epidemiology*, *39*(5), 358–363. http://doi.org/10.1007/s00127-004-0754-4**	X	
LEO (5)[2]	**Craig, T. K. J. (2004). The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*, *329*(7474), 1067–0. http://doi.org/10.1136/bmj.38246.594873.7C**	X	
	Gafoor, R., Nitsch, D., McCrone, P., Craig, T. K. J., Garety, P. A., Power, P., & McGuire, P. (2010). Effect of early intervention on 5-year outcome in non-affective psychosis. *The British Journal of Psychiatry: The Journal of Mental Science*, *196*(5), 372–376. http://doi.org/10.1192/bjp.bp.109.066050		X
	Garety, P. A., Craig, T. K. J., Dunn, G., Fornells-Ambrojo, M., Colbert, S., Rahaman, N., … Power, P. (2006). Specialised care for early psychosis: symptoms, social functioning and patient satisfaction. *The British Journal of Psychiatry*, *188*(1), 37–45. http://doi.org/10.1192/bjp.bp.104.007286	X	
	McCrone, P., Craig, T. K. J., Power, P., & Garety, P. A. (2010). Cost-effectiveness of an early intervention service for people with psychosis. *The British Journal of Psychiatry*, *196*(5), 377–382. http://doi.org/10.1192/bjp.bp.109.065896	X	
	Tempier, R., Balbuena, L., Garety, P., & Craig, T. J. (2012). Does assertive community outreach improve social support? Results from the Lambeth Study of early-episode psychosis. *Psychiatric Services (Washington, D.C.)*, *63*(3), 216–222. http://doi.org/10.1176/appi.ps.20110013	X	
OPUS (19)[3]	**Petersen, L., Nordentoft, M., Jeppesen, P., ØHLENSCHLÆGER, J., Thorup, A., Christensen, T. Ø., … Jørgensen, P. (2005). Improving 1-year outcome in first-episode psychosis OPUS trial. *The British Journal of Psychiatry, 187*(48), s98–s103.**	X	
	Stevens H, Agerbo E, Dean K, Mortensen PB, Nordentoft M. Reduction of crime in first-onset psychosis: a secondary analysis of the OPUS randomized trial. J Clin Psychiatry. 2013 May;74(5)	X	
	Petersen, L. (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*, *331*(7517), 602–0. http://doi.org/10.1136/bmj.38565.415000.E01	X	
	Thorup, A., Albert, N., Bertelsen, M., Petersen, L., Jeppesen, P., Le Quack, P., … Nordentoft, M. (2014). Gender differences in first-episode psychosis at 5-year follow-up--two different courses of disease? Results from the OPUS study at 5-year follow-up. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *29*(1), 44–51. http://doi.org/10.1016/j.eurpsy.2012.11.005		X
	Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlaeger, J., le Quach, P., … Nordentoft, M. (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of General Psychiatry*, *65*(7), 762–771. http://doi.org/10.1001/archpsyc.65.7.762		X
	Hastrup, L. H., Kronborg, C., Bertelsen, M., Jeppesen, P., Jorgensen, P., Petersen, L., … Nordentoft, M. (2013). Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *The British Journal of Psychiatry: The Journal of Mental Science*, *202*(1), 35–41. http://doi.org/10.1192/bjp.bp.112.112300		X
	Jeppesen, P., Petersen, L., Thorup, A., Abel, M.-B., Oehlenschlaeger, J., Christensen, T. Ø., … Nordentoft, M. (2005). Integrated treatment of first-episode psychosis: effect of treatment on family burden: OPUS trial. *The British Journal of Psychiatry. Supplement*, *48*, s85–90.	X	
	Nordentoft, M., Jeppesen, P., Abel, M., Kassow, P., Petersen, L., Thorup, A., … Jørgensen, P. (2002). OPUS study: suicidal behaviour, suicidal ideation and hopelessness among patients with first-episode psychosis. One-year follow-up of a randomised controlled trial. *The British Journal of Psychiatry. Supplement*, *43*, s98–106.	X	
	Nordentoft, M., Melau, M., Iversen, T., Petersen, L., Jeppesen, P., Thorup, A., … Jørgensen, P. (2015). From research to practice: how OPUS treatment was accepted and implemented throughout Denmark. *Early Intervention in Psychiatry*, *9*(2), 156–162.	X	
	Nordentoft, M., Øhlenschlæger, J., Thorup, A., Petersen, L., Jeppesen, P., & Bertelsen, M. (2010). Deinstitutionalization revisited: a 5-year follow-up of a randomized clinical trial of hospital-based rehabilitation versus specialized assertive intervention (OPUS) versus standard treatment for patients with first-episode schizophrenia spectrum disorders. *Psychological Medicine*, *40*(10), 1619–1626.		X
	Petersen, L., Jeppesen, P., Thorup, A., Øhlenschlæger, J., Krarup, G., Østergård, T., … Nordentoft, M.	X	

	(2007). Substance abuse and first-episode schizophrenia-spectrum disorders. The Danish OPUS trial. *Early Intervention in Psychiatry*, *1*(1), 88–96.		
	Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlaeger, J., Le Quach, P., … Nordentoft, M. (2009). Course of illness in a sample of 265 patients with first-episode psychosis--five-year follow-up of the Danish OPUS trial. *Schizophrenia Research*, *107*(2-3), 173–178		X
	Secher, R. G., Hjorthøj, C. R., Austin, S. F., Thorup, A., Jeppesen, P., Mors, O., & Nordentoft, M. (2015). Ten-Year Follow-up of the OPUS Specialized Early Intervention Trial for Patients With a First Episode of Psychosis. *Schizophrenia Bulletin*, *41*(3), 617–626.		X
	Thorup, A., Petersen, L., Jeppesen, P., & Nordentoft, M. (2010). The quality of life among first-episode psychotic patients in the opus trial. *Schizophrenia Research*, *116*(1), 27–34.	X	
	Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., … Nordentoft, M. (2005). Integrated treatment ameliorates negative symptoms in first episode psychosis--results from the Danish OPUS trial. *Schizophrenia Research*, *79*(1), 95–105.	X	
	Bergh S, Hjorthøj C, Sørensen HJ, Fagerlund B, Austin S, Secher RG, Jepsen JR, Nordentoft M. Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders, 10years after baseline: The OPUS study. Schizophr Res. 2016 Apr 2		X
	Madsen T, Karstoft KI, Secher RG, Austin SF, Nordentoft M. Trajectories of suicidal ideation in patients with first-episode psychosis: secondary analysis of data from the OPUS trial. Lancet Psychiatry. 2016 May;3(5):443-50.	X	
	Thorup, A., Petersen, L., Jeppesen, P., Øhlenschlaeger, J., Christensen, T., Krarup, G., … Nordentoft, M. (2006). Social network among young adults with first-episode schizophrenia spectrum disorders: results from the Danish OPUS trial. *Social Psychiatry and Psychiatric Epidemiology*, *41*(10), 761–770.	X	
	Wils RS, Gotfredsen DR, Hjorthøj C, Austin SF, Albert N, Secher RG, Thorup AA, Mors O, Nordentoft M. Antipsychotic medication and remission of psychotic symptoms 10years after a first-episode psychosis. Schizophr Res. 2017 Apr;182:42-48.		X
OTP (2)[4]	**Grawe, R. W., Falloon, I. R. H., Widen, J. H., & Skogvoll, E. (2006). Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatrica Scandinavica, 114*(5), 328–336.**	X	
	Sigrúnarson, V., Gråwe, R. W., & Morken, G. (2013). Integrated treatment vs. treatment-as-usual for recent onset schizophrenia; 12 year follow-up on a randomized controlled trial. *BMC Psychiatry*, *13*, 200.		X
PIANO (3)[5]	**Ruggeri, M., Bonetto, C., Lasalvia, A., Fioritti, A., de Girolamo, G., Santonastaso, P., … The GET UP Group. (2015). Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants. *Schizophrenia Bulletin*.**	X	
	Lasalvia A, Bonetto C, Lenzi J, Rucci P, Iozzino L, Cellini M, Comacchio C, Cristofalo D, D'Agostino A, de Girolamo G, De Santi K, Ghigi D, Leuci E, Miceli M, Meneghelli A, Pileggi F, Scarone S, Santonastaso P, Torresani S, Tosato S, Veronese A, Fioritti A, Ruggeri M; GET UP Group.. Predictors and moderators of treatment outcome in patients receiving multi-element psychosocial intervention for early psychosis: results from the GET UP pragmatic cluster randomized controlled trial. Br J Psychiatry. 2017 May;210(5):342-349.	X	
	Ruggeri M, Lasalvia A, Santonastaso P, Pileggi F, Leuci E, Miceli M, Scarone S, Torresani S, Tosato S, De Santi K, Cristofalo D, Comacchio C, Tomassi S, Cremonese C, Fioritti A, Patelli G, Bonetto C; GET UP Group. Family Burden, Emotional Distress and Service Satisfaction in First Episode Psychosis. Data from the GET UP Trial. Front Psychol. 2017 May 16;8:721	X	
RAISE-ETP (6)[6]	**Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, Addington J, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Meyer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Pipes R, Kurian BT, Miller AL, Azrin ST, Goldstein AB, Severe JB, Lin H, Sint KJ, John M, Heinssen RK. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry. 2015 Oct**	X	
	Rosenheck R, Leslie D, Sint K, Lin H, Robinson DG, Schooler NR, Mueser KT, Penn DL, Addington J, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Severe J, Rupp A, Schoenbaum M, Kane JM. Cost-Effectiveness of Comprehensive, Integrated Care for First Episode Psychosis in the NIMH RAISE Early Treatment Program. Schizophr Bull. 2016 Jul;42(4):896-906.	X	
	Rosenheck RA, Estroff SE, Sint K, Lin H, Mueser KT, Robinson DG, Schooler NR, Marcy P, Kane JM; RAISE-ETP Investigators.. Incomes and Outcomes: Social Security Disability Benefits in First-Episode Psychosis. Am J Psychiatry. 2017 Apr 21	X	
	Rosenheck R, Mueser KT, Sint K, Lin H, Lynde DW, Glynn SM, Robinson DG, Schooler NR, Marcy P, Mohamed S, Kane JM. Supported employment and education in comprehensive, integrated care for first	X	

	episode psychosis: Effects on work, school, and disability income. Schizophr Res. 2017 Apr;182:120-128.		
	Browne J, Penn DL, Meyer-Kalos PS, Mueser KT, Estroff SE, Brunette MF, Correll CU, Robinson J, Rosenheck RA, Schooler N, Robinson DG, Addington J, Marcy P, Kane JM. Psychological well-being and mental health recovery in the NIMH RAISE early treatment program. Schizophr Res. 2016 Nov 29.		
	Browne J, Penn DL, Bauer DJ, Meyer-Kalos P, Mueser KT, Robinson DG, Addington J, Schooler NR, Glynn SM, Gingerich S, Marcy P, Kane JM. Perceived Autonomy Support in the NIMH RAISE Early Treatment Program. Psychiatr Serv. 2017 Jun		
STEP (1)[7]	**Srihari, V. H., Tek, C., Kucukgoncu, S., Phutane, V. H., Breitborde, N. J., Pollard, J., … Woods, S. W. (2015). First-Episode Services for Psychotic Disorders in the US Public Sector: A Pragmatic Randomized Controlled Trial. *Psychiatric Services*.**	X	
JCEP (2)[8]	Hui, C. L. M., Chang, W. C., Chan, S. K. W., Lee, E. H. M., Tam, W. W. Y., Lai, D. C., … Chen, E. Y. H. (2014). Early intervention and evaluation for adult-onset psychosis: the JCEP study rationale and design. *Early Intervention in Psychiatry*, *8*(3), 261–268.	X	
	Hui CL, Lau WW, Leung CM, Chang WC, Tang JY, Wong GH, Chan SK, Lee EH, Chen EY. Clinical and social correlates of duration of untreated psychosis among adult-onset psychosis in Hong Kong Chinese: the JCEP study. Early Interv Psychiatry. 2015 Apr;9(2):118-25. doi: 10.1111/eip.12094. Epub 2013 Sep 30.	X	
Integrated treatment to functional recovery Study 1: Valencia 12 Months (1)[9]	Valencia, M., Juarez, F., & Ortega, H. (2012). Integrated Treatment to Achieve Functional Recovery for First-Episode Psychosis. *Schizophrenia Research and Treatment*, *2012*, e962371.	X	
Integrated treatment to functional recovery Study 2: Valencia 6 Months (1)[10]	Valencia M, Juarez F, Delgado M, Díaz A. Early Intervention to Improve Clinical and Function-al Outcome in Patients with First Episode-Psychosis. In: *Mental Disorder*. Vol Hong Kong: iConcept Press; 2014	X	

Supplement 7: eTable 2. **Detailed Study, Patient and Treatment Characteristics of Included Studies**

Program Name	**Croydon Outreach and Assertive Support Team (COAST)**[1]	**The Jockey Club Early Psychosis (JCEP)**[2]	**Lambeth Early Onset (LEO)**[3]	**Specialized assertive intervention (OPUS)**[4]	**Optimal Treatment Project (OTP)**[5]	**Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)**[6]	**Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)**[7]	**Specialized Treatment Early in Psychosis (STEP)**[8]	**Integrated treatment to functional recovery, Study 1**[9]	**Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)**[10]	**Summary**
Funding	UK Department of Health	Hong Kong Jockey Club Charities Trust	Directorate of Health and Social Care London research and development organisation and management programme	Danish Ministry of Health, Ministry of Social Affairs, University of Copenhagen, Copenhagen Hospital Corporation, Danish Medical Research Council, Slagtermester Wørzners Foundation	Norwegian Research Council; Norwegian Ministry of Health	Italian Ministry of Health	US National Institute of Mental Health (NIMH)	US National Institute of Mental Health (NIMH), Donaghue Foundation	Mexican National Institute of Psychiatry Ramón de la Fuente Muñiz	Mexican National Institute of Psychiatry Ramón de la Fuente Muñiz	National government funding agency=8; Local/foundation funding agency:2
Duration (time points assessments) months	9 (0, 6, 9)	24 (0, 6, 12, 24)	18 (0, 18)	24 (0, 12, 24)	24 (0, 12, 24)	9 (0, 9)	24 (0, 6, 12, 18, 24)	12 (0, 12)	12 (0, 12)	6 (0, 6)	16.2±7.4 (median=15, range=6-24).
# of Sites / Location	1, South London/UK	1, Hong Kong	1, London/UK	5, Denmark	1, Norway	117, Italy	34, US	1, US	1, Mexico	1, Mexico	Europe: studies=5, n=1,244; US: studies=2, n=524; Mexico: studies=2, n=208; Hong Kong: study=1, n=200
Primary Outcome(s)	Not specified	Global functioning	Relapse; Readmission	Psychotic and negative symptom severity	Remission; Psychotic and negative symptom severity	Symptom severity; Days of Hospitalization	Quality of Life	Hospital Utilization; Vocational engagement; Global functioning	Not specified	Not specified	Not specified: studies=4; Hospitalization/ Hospital Utilization/ Readmission: studies=3; Psychotic symptom severity: studies=2; Relapse=1; Remission=1; Negative symptom severity=1;

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
											Quality of Life=1; Vocational engagement=1; Global functioning=1
N baseline (EIS, TAU)	59 (32/27)	200 (100/100)	144 (71/73)	547 (275/272)	50 (30/20)	444 (272/172)	404 (223/181)	117 (60/57)	88 (44/44)	120 (60/60)	2,173 (1,167/ 1,006)
Early intervention services Components	Medication review; vocational/ educational counseling; CBT; family PE/counseling; family therapy; crisis response team/ crisis management	Medication review; vocational/ educational counseling; CBT; family PE/counseling; crisis response team/ crisis management; SST	Medication review; vocational/ educational counseling; CBT; family PE/counseling	Medication review; family PE/counseling; family therapy; crisis response team/ crisis management; SST	Medication review; CBT; family PE/counseling; family therapy; crisis response team/ crisis management; SST	Medication review; CBT; family PE/counseling; family therapy	Medication review; vocational/ educational counseling; CBT; family PE/counseling	Medication review; vocational/ educational counseling; CBT; family PE/counseling; family therapy	Medication review; family PE/counseling; family therapy; SST	Medication review; family PE/counseling; family therapy; SST	Medication review: studies=10; family PE/counseling: studies=10; CBT: studies=7; family therapy: studies=7; vocational/ educational counseling: studies=5; SST: studies=5; crisis response team/crisis management: studies=4

Program Name	**Croydon Outreach and Assertive Support Team (COAST)**[1]	**The Jockey Club Early Psychosis (JCEP)**[2]	**Lambeth Early Onset (LEO)**[3]	**Specialized assertive intervention (OPUS)**[4]	**Optimal Treatment Project (OTP)**[5]	**Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)**[6]	**Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)**[7]	**Specialized Treatment Early in Psychosis (STEP)**[8]	**Integrated treatment to functional recovery, Study 1**[9]	**Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)**[10]	**Summary**
EIS treatment (offered)	Needs based: CBT, PE, family meetings and intervention, vocational support. Additionally medication review and crisis response management	Needs based: PE, family PE/ intervention, individual reintegration (30min each, weekly); CBT, individual intervention, SST (50min each, weekly), PT group, reintegration group (90min each, weekly). Additionally medication review and crisis response management	Needs based: CBT; family counseling; vocational support Additionally medication review	Needs based: ACT including medication review, family involvement (bi-weekly multiple family groups à 120min) and SST. Additionally crisis response management	Month 1-2: weekly sessions à 60min; month 3-24: ≥1 session à 60min/ 3 wks; when crisis/ exacerbation: < 3 sessions/ wk plus with telephone consultation. Additionally medication review, CBT, family therapy/ counseling, SST and crisis response management	CBT: 20-30 sessions per patient (month 1-3 weekly; month 4-9 bi-weekly; family intervention: 10-15 sessions with each individual family (month 1-3: 6 sessions; month 4-9: ≥1 session/ month Additionally medication review	Needs based: IRT, family PE, and vocational counseling. Additionally computer-assisted medication review/management	Weekly CBT sessions (48x); family PE: individual families (3x) and multi-family groups (bi-weekly) Additionally medication review and educational counseling	CBT weekly (48x60min); group sessions weekly (48x75min); PE in multifamily group sessions (10x); Family counseling (problem solving and improving communication skills, 4x); monthly medication reviews (6x20min)	CBT weekly (24x60min); group sessions weekly (24x90min); PE in multifamily group sessions (8x); Family counseling (problem solving and improving communication skills, 4x); monthly medication reviews (6x20min)	
EIS treatment (attended)	Intensity/ frequency of usage not assessed.	Intensity/ frequency of usage not assessed.	Number of appointments: 17.4±9.1 (18 months) CBT: n=30 (54.9%); family counseling: n=40 (56.3%), vocational support: n=36 (50.7%)	Outpatient contacts: 45.3/yr, family involved: 59% (1st yr); Outpatient contacts: 31.9/yr Family involved: 42% (2nd yr)	Intensity/ frequency of usage not assessed.	CBT: 1-4 sessions: n=15 (5.5%), 5-9 sessions: n=25 (9.2%), 10-19 sessions: n=70 (25.8%), 20+ sessions: n=138 (50.7%). No CBT: n=24 (8.8). Mean number of CBT sessions: 18.8±10.3 (0-44) Family	Services used/ month: 4.5±5.1 IRT: n=208 (93.3); family PE: n=159 (71.3); SEE: n=187 (83.9) Average number of sessions/yr: IRT =22.1; family PE=13.8 ±15.0; SEE=13.6 Intensity of other components not	Psychiatrist visits: 0.4/month; other clinician visit: 1.1/month; visiting nurse: 0.8/month	Intensity/ frequency of usage not assessed.	Intensity/ frequency of usage not assessed.	

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
						intervention sessions: 1-4 sessions: n=24 (8.8%), 5-9 sessions: n=56 (20.6%), 10-19 sessions: n=120 (44.1%), 20+ sessions: n=20 (7.3%). No Family intervention: n=52 (19.2%). Mean number of Family intervention sessions: 9.3±7.0 (0-36) Case management contacts: 1-4 contacts: n=96 (35.3%), 4-9 contacts: n=40 (14.7%), 10-19 contacts: n=59 (21.7%), 20+ contacts: n=77 (28.3%). No case management contact: n=0 (0.0%) Mean number of case management contacts:	separately assessed.				

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
						21.7±24.4 (1-120) Nonspecific interventions (patients): n=68 (27.3%), nonspecific interventions (families): n=25 (20.8%)					
Caseload EIS vs. TAU	EIS: <12 patients per care-coordinator; TAU: 35 patients per keyworker	EIS: <80 patients per case manager; TAU: 80-100 patients per case manager 1:80	NR	EIS: 10 patients per case manager; TAU: 20-30 per case manager	EIS: 10 patients per case manager	NR	NR	50 patients per clinician	NR	NR	
TAU treatment (offered)	Local multidisciplinary team; medication, monitoring and access to services, but no specialized psychological interventions, nor information geared towards early intervention issues.	Multidisciplinary intervention team services including specialist out-patient clinics, in-patient facilities, day hospital and community outreach services.	Routine community mental health services comprising psychiatrists, psychologists and community psychiatric nurses. No additional training in the management of early psychosis. Encouragement to follow guidelines.	Treatment at a community mental health center. Always contact with a physician, a community mental health nurse, and sometimes with a social worker. No information on PT available. The medication was based on the same principles as in the integrated treatment.	Regular clinic-based case management with AP drugs, supportive housing and day care, crisis in-patient treatment, rehabilitation promoting independent living and work, brief PE, and supportive PT. Pharmacotherapy and case management alike EIS but with higher case-load.	Standard care at Community mental health centers: Personalized outpatient psychopharmacological treatment and psychosocial management by a multi-professional mental health team. No case management formats.	Community care: Psychosis treatment by clinician choice and service availability. No additional training or supervision. Sites had capacity to be trained to provide EIS and the willingness to do so	Community treatment based on patients' insurance (either existing outpatient treatment or referral based on health insurance). No specialized intervention.	Monthly medication review (12x20min) No other general psychiatric interventions or specialized interventions as CBT, multi-family groups etc.	Monthly medication review (6x20min) No other general psychiatric interventions or specialized interventions as CBT, multi-family groups etc.	
TAU treatment	Not assessed	Not assessed	Number of	Outpatient	Not assessed	Nonspecific	Services used/	Psychiatrist visits:	Not assessed	Not assessed	

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
(attended)			appointments: 13.2±8.7 (18 months) CBT: n=20 (27.4); family counseling: n=17 (23.3), vocational support: n=17 (23.3)	contacts: 17.5/yr, family involved: 18% (1st yr); Outpatient contacts: 10.5/yr Family involved: 9% (2nd yr)		interventions (patients): n=66 (49.3%), nonspecific interventions (families): n=34 (25.4%)	month: 3.7±5.9; family PE: n=73 (40.3), number of sessions=4.39±5.57 Intensity of other components not separately assessed.	0.2/month; other clinician visit: 0.8/month; visiting nurse: 0.6/month			
Treatment compliance (%)	Not assessed	Not assessed	EIS: n=53 (74.6); TAU: n=44 (60.3)	EIS: n=254 (96.6); TAU: n=205 (84.0) (based on records available for 507/547 patients)	EIS: 27 (90.0); TAU: 16 (80.0)	EIS: 247 (90.8%); TAU: 157 (91.3%) ("in contact with service at follow-up")	Not assessed	Not assessed	EIS=87.2	EIS=86.4	
Medication adherence (%)	Not assessed	Not assessed	EIS=month 1: n=71 (100.0), (71/71), month 6: n=45 (63.4); month 12: n=31 (43.7), month 18: n=43 (60.6)	EIS=year 1: 68%, year2: 60%; TAU=year 1: 61%, year 2: 55%	Patients who had problems adhering to oral medication were offered depot injections (EIS: 20%; IT: 23%)	Not assessed	Not assessed	Not assessed	EIS=85.0; TAU=67.6	EIS=88.9; TAU=82.5	
Inclusion Criteria	1st episode of any functional psychosis in past 5 years of contact	FEP according to DSM IV	≤2 episodes of non-affective psychosis: SCZ; SzT; delusional disorder	1st episode SCZ spectrum d/o including DEL and SzT; ≤12 weeks AP medication	Recent onset SCZ (≤2 years since FEP) more than 1 acute episode	1st lifetime contact with the center for any functional PSY	FEP (SCZ-spectrum; psychosis NOS, brief psychosis), ≤6 months AP medication	FEP (non-affective); ≤5 years ago; ≤12 weeks AP medication	FEP (SCZ); stable after first AP medication (≥15 days); no substance abuse	FEP (SCZ); stable after first AP medication (≥15 days); no substance abuse	FEP=2, first episode SCZ-spectrum d/o=7, recent onset SCZ (<2 years) with >1 episode; stable after first AP medication (≥15 days)=2, ≤3 months AP use, ≤6 months AP use=1; no substance abuse=2

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
STUDY AND DATA CHARACTERISTICS											
Fidelity Monitoring: Internal supervision	"Skills were assessed and monitored"	"Regular in-house trainings" "Weekly supervisions with experienced clinicians and clinical psychologist",	"Adherence to treatment protocols ensured through supervision of CBT, medication prescribing, family support, and the assertive outreach model"	"Adherence to treatment protocols ensured through a training program and external supervision of CBT, social skills training and family involvement. Weekly internal supervision of ACT."	"Regular contact between the research team and the clinical teams enabled adherence to both treatments". "weekly case supervision" "annual review of the quality treatment by an independent researcher"	"The staff was trained for 6 months for CBT, family intervention and case management and supervised by experts" "Supervision of written reports of each session by external experts" "audio-recording of a random sample of sessions to allow further fidelity measurement by independent raters."	"Initial training in team-based first-episode psychosis interventions, and ongoing expert consultation" "Continuous assessments of clinicians' competence and monitoring of team functioning."	"Weekly supervision of clinicians providing CBT (group and individual) and family education (group and individual) by expert psychologist. Weekly case-based supervision of clinicians at team rounds."	"Before treatment, competency levels had to be demonstrated with at least a 90 percent level of efficacy." "A therapist evaluation form was used to verify that all treatment areas were conducted properly." "Therapists' competency during treatment was assessed by a specially trained research assistant." "Monitoring for maintenance of fidelity occurred throughout the study."	"Before treatment, competency levels had to be demonstrated with at least a 90 percent level of efficacy." "A therapist evaluation form was used to verify that all treatment areas were conducted properly." "Therapists' competency during treatment was assessed by a specially trained research assistant." "Monitoring for maintenance of fidelity occurred throughout the study."	
Fidelity Monitoring: Scalable Outcome Assessments	No external and/or standardized fidelity monitoring.	No external and/or standardized fidelity monitoring.	No external and/or standardized fidelity monitoring.	IFACT (Index of fidelity): 70%. Reasons lower fidelity: limited treatment, 24h coverage, <two contacts/ week with patient/	CSI (Clinical Strategies Implementation Scale): data not available	CTS-R: Cognitive Therapy Scale-Revised; CTPAS: Cognitive Therapy for Psychosis Adherence Scale; ad hoc checklists	Fidelity index: 2.51±0.30 (1-3); 52.9%: good implementation; 47.1%: basic implementation. Ratings include all components	No external and/or standardized fidelity monitoring.	TEF (Therapy evaluation form): data not available	TEF (Therapy evaluation form): data not available	Scalable Outcome Assessments: studies=6; n=1653; Outcomes reported: studies=3; n=1395

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
				family/partners		based on the specific trial intervention: Professionals' fidelity was rated medium to high.	and the overall organization of the team				
Blinded Outcome Assessments	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Blinded Outcome Assessments: studies=7, n=1,050
Data type and statistical Analysis Methods	ITT, linear and ordinal logistic regression	ITT, linear and logistic regression, cox proportional hazard regression	Endpoint data, logistic regression	ITT, repeated measurements model with unstructured variance matrix, logistic regression, analysis of variance	ITT, general linear model, repeated measures analysis of variance	Endpoint data, multilevel mixed-model analyses, weighted random effects linear regression model	ITT, mixed-effects linear regression model	ITT/ endpoint data (depending on outcome), logistic and linear regression models, analysis of covariance	Endpoint data, analysis of variance	Endpoint data, analysis of variance	ITT: studies=6, randomized: n=1.380, analyzed=1.359; Endpoint data: studies=5, randomized: n=916, analyzed: n=784
Attrition at endpoint (%): overall (EIS; TAU)	66.1 (EIS=65.6; TAU=66.7)	4.0 (EIS=4.0; TAU=4.0)	32.6 (EIS=25.4; TAU=39.7)	32.5 (EIS=25.5; TAU=39.7)	0.0 (EIS=0.0; TAU=0.0)	11.7 (EIS=12.1, TAU=11.0)	42.8 (EIS=34.1; TAU=53.6)	22.2 (EIS=20.0; TAU=24.6)	17.0 (EIS=11.4; TAU=22.7)	15.0 (EIS=10.0; TAU=20.0)	25.9 (EIS=21.3; TAU=31.3)
Reasons for study drop-out EIS	Refusal/ unable to reach: n=21	Unable to reach: n=2; death: n=2 No drop-out for inefficacy or adverse effects.	Notes missing or lost to follow-up: n=2	Incomplete records: n=12 (suicide: n=1; moved away: n=7; lost to follow-up: n=4); patients without follow-up interview: n=36 (refused/ did not turn up: n=32; moved far away: n=4)	No drop-outs	Lost to follow-up: n=27; refused: n=5; death: n=1	Lost to follow-up: n=25; personal reasons: n=19; moved out of area: n=15; didn't want to continue study: n=11; didn't want to continue treatment: n=4; incarcerated: n=2	Unable to reach: n=6; referred away: n=4; incarcerated: n=1; moved out of state: n=1	Lost to follow-up: n=5	Lost to follow-up: n=6	

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
Reasons for study drop-out TAU	Refusal/ unable to reach: n=22	Unable to reach: n=3; death: n=1 No drop-out for inefficacy or adverse effects.	Notes missing or lost to follow-up: n=5, death: n=1	Incomplete records: n=28 (suicide: n=1; unexpected death: n=1; death by accident: n=1; moved away: n=12; lost to follow-up: n=13); patients without follow-up interview: n=58 (refused/ did not turn up: n=51; moved far away: n=1)	No drop-outs	Lost to follow-up: n=19; refused: n=4; death: n=2	Lost to follow-up: n=45; personal reasons: n=7; moved out of area: n=20; didn't want to continue study: n=14; incarcerated: n=10; unknown: n=1	Unable to reach: n=11; incarcerated: n=1; moved out of state: n=1	Lost to follow-up: n=10	Lost to follow-up: n=12	
PATIENT CHARACTERISTICS											
Age (range)	28±8 (18-65)	36.6±8.7 (26-55)	26.3±6.2 (16-40)	26.6±6.4 (18-45)	25.4±4.6 (18-35)	30.2±9.6 (18-54)	23.1±5.1 (16-45)	22.5±4.9 (16-45)	24.3±3.1 (16-50)	26.8±5.0 (16-50)	Mean (weighted): 27.5±4.6 (range=16-65)
Male: %	75	43	65	59	62	59	73	98	75	66	Mean (weighted): 62.3
ILLNESS CHARACTERISTICS											
Diagnosis: %	SCZ/SzA: 83.1; BP: 12.5; Substance induced PSY: 1.0	SCZ: 44.0; SzF: 17.0; Brief PSY: 12.0; PSY NOS: 6.0; SzA: 1.0	SCZ: 69.4	SCZ: 66.2; SzT: 14.4; Brief PSY: 8.2; SzA: 4.6; DEL: 4.6; PSY NOS: 2	SCZ: 80; SzA: 12; SzF: 8	SCZ: 27; Brief PSY: 18; DEL: 16; Mania with PSY: 13; MDD with PSY: 9; SzA: 9; PSY NOS: 6; SzT: 2	SCZ: 52.9; SzF: 16.6; SzA depressive: 14.1; PSY NOS: 9.9; SzA BP: 5.9; Brief PSY: 0.5	SCZ or SzA: 29.0	SCZ: 100.0	SCZ: 100.0	Percentage (total sample): SCZ: 55.8; PSY NOS: 8.8; SzA: 7.3; Brief PSY: 7.0; DEL: 6.0; SzF: 5.9; SzT: 4.0; BP/ Mania with PSY: 2.9; MDD with PSY: 1.9; substance-induced PSY: 0.3
DUP (wks): mean (median)	NR	73.6 (13.3)	9.1 (16.0)	NR	NR	45.2 (8.0)	193.5 (74.0)	43.9 (12.0)	NR	NR	Mean (weighted): 79.9±71.1; Mean (unweighted) of medians: 24.9±27.6) wks
Prior AP	NR	15.6	37.9	NR	NR	0.2	6.1	NR	NR	NR	Mean (weighted):

Program Name	Croydon Outreach and Assertive Support Team (COAST)[1]	The Jockey Club Early Psychosis (JCEP)[2]	Lambeth Early Onset (LEO)[3]	Specialized assertive intervention (OPUS)[4]	Optimal Treatment Project (OTP)[5]	Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	Specialized Treatment Early in Psychosis (STEP)[8]	Integrated treatment to functional recovery, Study 1[9]	Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	Summary
treatment (wks)											6.7±16.6; Median: 10.8
No of prior hospitalizations per patient (mean)	NR	0.59	0.16	NR	NR	0.0	0.79	0.90	1.16	1.27	Mean (weighted): 0.46±0.48
FUNCTIONING											
GAF (baseline)	NR	NR	44.6	41.3	49.8	44.9	NR	35.3	44.4	43.6	Mean (weighted): 42.9 ±4.4
Employed/ School: % of patients (baseline)	NR	53.5	31.9	30.8	NR	35.8	34.7	57.0	31.5	28.4	Mean (weighted): 37.0±11.5

Duration of untreated psychosis (DUP)=defined as the time interval between the onset of positive psychotic symptoms and the first appropriate treatment)
ACT=Assertive community treatment; AP=antipsychotic; BL=baseline; CBT=Cognitive Behavioral Therapy; CDSS=Calgary Depression Scale for Schizophrenia; CGI=Clinical Global Impression Scale; DEL=delusional disorder; DUP=Duration of Untreated Psychosis; EIS=Early Intervention Services; FEP=first episode of psychosis; GAF=global assessment of functioning; m=month(s); ITT=Intention-to-treat; IRT=individual resilience training; MH=Mental Health; N=number of patients (randomized); No=Number; NOS=not otherwise specified; NR=not reported; n.s.=not significant; OC=observed cases; PANSS=Positive and Negative Symptom Scale; PE=Psychoeducation; PSY=Psychosis; QLS=Quality of Life Scale, SEE=supported employment and education; SCI=Specialty Care Intervention; SCZ=schizophrenia; SST=Social Skills Training; SzA BP=Schizoaffective Bipolar; SzA DEP=Schizoaffective Depressive; SzF=schizophreniform disorder; SzT=schizotypal disorder; TAU=treatment as usual; tx=treatment; yr(s)=year(s), wks=weeks, m=month(s)

Supplement 8: eTable 3. **Detailed information on EIS interventions and standard treatment comparator**

Program Name	Program Details
Croydon Outreach and Assertive Support Team (COAST)[1]	The COAST service consisted of a Team Leader (with a social work background), 3.5 whole time equivalent (wte) care co-ordinators (with nursing and occupational therapy backgrounds), 0.5 wte clinical psychologist, 0.3 wte consultant psychiatrist and one session per week of family therapist time. Caseloads were low (no more than 12 cases per care co-ordinator). Beginning functioning in April 2000, it predated but closely adhered to the service model set out in the Policy Implementation Guide (Department of Health 2001). The service was available 7 days per week, with night cover provided by Croydons Crisis Response Nursing Team. A range of interventions was offered to participants who were randomised to COAST. Interventions were offered flexibly and as needed, not via a protocol. All participants were offered medication review and monitoring, vocational and benefits help, information about psychosis, individual therapy for residual positive symptoms of psychosis (CBT) (based on Fowler et al. 1995), family meetings and intervention if appropriate, based on Kuipers et al. (2002). Supervision and support were available for both of these interventions, by a team clinical psychologist, Dr Kathy Kavanagh, and a carer's support worker, Wendy Maphosa, respectively, offered at least fortnightly. The whole team was given training in all relevant interventions. Skills learnt were assessed and monitored and are reported separately (Slade et al. 2003). *People offered TAU* remained with their referring team, and were offered all the usual services available to a local multidisciplinary team; medication, monitoring and access to services, but no specialized psychological interventions, nor information geared towards early intervention issues. Caseloads were high (average 35 per keyworker).
The Jockey Club Early Psychosis (JCEP)[2]	JCEP clinical process is a cycle of engagement, assessment, case formulation, intervention and outcome review. (1) *Engagement*: the case intervention officers engage the patients and their care givers in a collaborative relationship which allows the patient to seek help whenever they have needs. Case intervention officers also aim to provide in-depth understanding to cultivate trusting relationship with the patients. (2) *Assessment and case formulation:* Case formulation is one of the most important processes that lead to the construction of an individualized care plan for first episode psychosis patients in JCEP. The case formulation process involves identifying and understanding the key factors contributing to a patient's illness. Clinical formulation could be at the levels of biological, cognitive, psychological, family and relational levels. Factors from these levels interact in their expression as problems and symptoms. A competent formulation is essential for an effective and individualized intervention strategy. (3) *Intervention options/components*: Each patient receives a designated JCEP intervention officer to personally engage, evaluate, plan and follow the initial, often eventful, years of the disorder. JCEP adopted an individualized phase-specific case management approach in intervention which allows the formulation of patients' care plan. The approach is comprised of five service components which have different intervention objectives and goals according to patients' stage of illness. Depending on individual's needs and stage of illness, different psychological treatments including cognitive-behavioral therapy, psychoeducation, skills training, crisis intervention, relapse prevention, and stress management will be applied. The *table* below summarizes the various intervention components and illness stages. In the JCEP service, the multidisciplinary intervention team including psychiatrists, psychiatric nurses, social workers and clinical psychologists worked closely together to serve different catchment areas covering the entire population in Hong Kong. Treatments follow a framework according to Hospital Authority guideline for early Psychosis (The Hospital Authority, 2010). Psychological intervention follows a specific protocol (PIPE; So, 2013). JCEP has also developed an intervention manual specifically tailored for the needs of adult psychosis patients. The frequency of contacts is mainly decided by clinical stage. Generally, in the initial stage of rapport building and need assessment, case intervention officers contact the patients more frequently. Frequent contacts are provided for crisis intervention or handling relapse situation. Intervention officers also take a more active role for those patients with low motivation or poor insight on compliance with the treatment plan. Unfortunately, we do not have the actual utilization statistics for each of the components. In addition, there were 5 patients (5 of 100, 5%) in the intervention group who did not take antipsychotics medication at baseline (study entry). Patients in the *standard care group* receive standardized outpatient and inpatient general psychiatric service in

	Hong Kong. The standard care service is also a multidisciplinary intervention team which provides a spectrum of services including specialist out-patient clinics, in-patient facilities, day hospital and community outreach services. The service is delivered based on a Clinical Practice Guideline for Management of Schizophrenia (The Hospital Authority, 2010). The guideline was developed in 2004 and updated in 2010 by a group of experienced psychiatrists in Hong Kong.
Lambeth Early Onset (LEO)[3]	The Lambeth Early Onset (LEO) Team was a multidisciplinary community team comprising 10 members of staff including two psychiatrists (one in training), 1 clinical psychologist, 1 occupational therapist, 4 community psychiatric nurses and 2 health care assistants. The community psychiatric nurses had caseloads of approximately 1:18. The psychiatrist(s) saw all patients. It operated an assertive community treatment intervention providing a single point of access for all the mental health and social welfare needs of their patients with an extended hours service (8am-8pm) 5 days/week and 9am-5pm at week-ends and public holidays. Following the principles of assertive community treatment, patients who were reluctant to participate were regularly followed up and efforts made to motivate the patient to accept support and treatment. The frequency of contact varied according to how well the person was engaged with the service and apparent recovery but was typically weekly for the first 4-6 weeks tapering subsequently but never less than monthly. All patients had an active care plan (including for possible crises) and were given an out-of-hours emergency telephone contact to a member of the LEO team. The interventions provided by the team were a pragmatic mix of routinely available medication management, cognitive behavioural therapy for psychosis (CBTp) and family support. Medication protocols were for the use of neuroleptics based on those developed by the EPPIC service in Melbourne Australia. The emphasis of the whole programme was on helping the patient retain or recover functional capacity to return to study or work, to resume leisure pursuits and supportive networks. A family / carers support group was established as was a social activity programme open to all patients in the service. The *standard care comparison* was provided by routine community mental health services in the same geographical location, these services comprised psychiatrists, psychologists and community psychiatric nurses. While routinely including those with a first episode of psychosis, these teams managed a broad spectrum of patients with differing diagnoses and durations of illness. Community psychiatric nurses had caseloads of approximately 1:30. Most contacts were made in community mental health centres although home visits could be provided in response to a crisis. In principle, all patients had access to the same array of medical and psychological interventions as did the LEO team. These teams received no special training or support in the management of early psychosis, though they were not discouraged from following best practice guidelines which were nationally available and in principle expected to be followed as best practice.
Specialized assertive intervention (OPUS)[4]	OPUS treatment consisted of assertive community treatment enhanced by better specific content via family involvement and social skills training. Two multidisciplinary teams in Copenhagen and one in Aarhus were established and trained to provide integrated treatment. Caseload reached a level of about 10. Each patient was offered OPUS treatment for a period of two years. A primary team member was designated for each patient and was then responsible for maintaining contact and coordinating treatment within the team and across different treatment and support facilities. Patients were visited in their homes or other places in their community or at their primary team member's office according to their preference. During hospitalization, treatment responsibility was transferred to the hospital, but a team member visited the patient once a week. The office hours were Monday to Friday, 8 am to 5 pm. All team members had a mobile phone with an answering function. Outside office hours, patients could leave a message and be sure that the team would respond the next morning. A crisis plan was developed for each patient. If the patient was reluctant about treatment, the team stayed in contact with the patient and tried to motivate the patient to continue treatment. The fidelity of the program, measured with the index of fidelity of assertive community treatment, was 70% in both Copenhagen and Aarhus. The factors responsible for the reduced fidelity were time limited treatment, 24-hour coverage in other settings, and about two contacts weekly with each patient, patient's family, and collaborating partners. Psychoeducational family treatment was offered, and team members always tried to make contact with at least one family member and motivate patients and families to participate in a psychoeducational group. Family treatment followed McFarlane's manual for psychoeducational treatment for multiple family groups and included 18 months of treatment, 1.5 hours every second week, in a multiple family group with two therapists and four to six patients with their families. The multiple family group focused on problem solving and development of skills to cope with the illness. Patients' social skills were assessed using the World Health Organization's psychiatric disability assessment. Patients with impaired social skills were offered social skills training focusing on medication, coping with

	symptoms, conversation, and problem-solving skills in a group of maximum six patients and two therapists. *Standard treatment* usually offered the patient treatment at a community mental health center. Each patient was usually in contact with a physician, a community mental health nurse, and in some cases also a social worker. Home visit was possible, but office visits were the general rule. A staff member's caseload in the community mental health centers varied between 1:20 and 1:30. Outside office hours, patients could refer themselves to the psychiatric emergency room.
Optimal Treatment Project (OTP)[5]	Patients in the Integrated Treatment group (IT) were treated by a multi-disiplinary team that was independent of the standard treatment (ST) programme. Pharmacotherapy and case management was similar to ST with a low case-load (patient-sta□ ratio approximately 1 : 10). In addition IT cases received structured family psychoeducation, cognitive–behavioural family communication and problem solving skills training, intensive crisis management provided at home, and individual cognitive-behavioural strategies for residual symptoms and disability. This approach is described in several published manuals and is almost identical to that advocated as optimal treatment for schizophrenia in recent international guidelines and reviews. Treatment sessions were held in the home and were tailored in content and frequency to the individual goals and needs of patients and their key carers. In most cases weekly hour-long sessions were provided during the first 2 months and thereafter at least one session every third week for the first year then at least one session monthly during the second year of the project. In periods of crisis and exacerbations, intensive home-based sessions were provided up to three times a week, often supplemented with telephone consultation. The dose of antipsychotic medication was kept to the lowest e□ective level taking into consideration the sensitivity of recent-onset patients to medication side e□ects. Monotherapy was preferred and plasma assays were frequently used to optimise dose and to check adherence. Patients, who had problems adhering to oral medication despite education and problem solving, were o□ered depot injections (20% in ST group, 23% in IT group). For the 20% of the patients who had less than weekly contact with any informal carers, educational and problem solving training sessions were conducted in individual sessions. Treatment in both conditions was goal and problem oriented and no attempt was made to match the dose of biomedical or psychosocial interventions. Regular contact between the research team and the clinical teams enabled the adherence to both treatments to be assessed. In addition to weekly case supervision, an annual review of the quality of IT treatment was conducted by an independent researcher (IRHF) (34). *Standard treatment*: ST patients received regular clinic-based case management with antipsychotic drugs, supportive housing and day care, crisis in-patient treatment at one of two psychiatric hospitals, rehabilitation that promoted independent living and work activity, brief psychoeducation, and supportive psychotherapy. 16 (80%) of the patients received ST from hospital out-patient services and the remainder from local community general health services.
Psychosis: early Intervention and Assessment of Needs and Outcome (PIANO)[6]	*The experimental treatment* package was provided by routine public Community Mental Health Centers (CMHCs) which operate within the Italian National Health Service and consisted of standard care (treatment as usual, TAU, see below) plus evidence-based additional treatment. Specifically, the multi-element psychosocial intervention, adjunctive to TAU, comprised: (i) Cognitive Behavioural Treatment for psychosis (CBTp) to patients; (ii) psychosis-focused Family Intervention (FIp) to individual families; and (iii) Case Management (CM) to both parties. CBTp was based on the model developed by Kuipers et al, Garety et al and Fowler et al; the model has already been evaluated in randomized controlled trials. An optimal number of 20-30 CBT sessions per patient was expected to be delivered over a time frame of 9 months, with weekly sessions held during the first three months and fortnightly over the following 6 months. FIp was based on the model proposed by Leff et al and further developed by Kuipers et al. It included an optimal number of 10-15 sessions over 9 months, with each individual family: 6 sessions in the first three months, and at least 1 session/month in the 6 months afterwards. Every patient/family had a dedicated CM, who coordinated all planned interventions. Experimental interventions were expected to begin as soon as the patient was stabilized (clinical stabilization was defined as a condition allowing the patient to collaborate in at least a brief clinical examination) and after he/she has been assessed with the 'core' set of baseline measures. Professionals applying the experimental interventions received specific training programs in CBTp, FIp and CM. At the end of the training, an assessment of the competence achieved was performed and detailed intervention Manuals, based on international standards, were developed and given to the professionals as a standard to be followed for their treatment. Professionals were supported in their clinical work by a team of expert psychotherapists assigned to each CMHC. Moreover, experimental interventions provided to all patients/relatives were supervised by a team of external experts who held one day meetings every two months and were regularly available for consultation.

	Fidelity was measured at the end of the trial by an independent team by using audio-tape recordings of therapy sessions, and therapists ratings of their own session. The Cognitive Therapy Scale-Revised (CTRS) and the Cognitive Therapy for Psychosis Adherence Scale (CTPAS) were used, together with ad hoc checklists based on the specific trial intervention Manuals, according to the method described in McHugo et al. *Treatment as usual* (TAU) was also provided by routine public Community Mental Health Centers (CMHCs), which operate within the Italian National Health Service, involved in the Trial. In Italy standard care for FEP patients typically consists of personalized outpatient psychopharmacological treatment, combined with psychosocial management by a multi-professional mental health team, whose intensity and organization may vary locally, but that is not usually formalized in case management formats. Having as less as possible hospital admissions for FEPs is the norm, rather than the exception.
Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP)[7]	The experimental treatment, NAVIGATE, includes four core interventions: personalized medication management (assisted by COMPASS, a secure, web-based decision support system developed for RAISE-ETP); family psychoeducation; resilience-focused individual therapy; and supported employment and education (SEE). Treatment was supported through existing funding mechanisms except for SEE, which is not supported in many locations. SEE services (5 hours/ week) were supported with research funds. Treatment components were offered and implemented within a shared decision-making, patient-preference framework (20). Weekly team meetings facilitated communication and coordination. NAVIGATE sites received initial training in team-based first-episode psychosis interventions, and ongoing expert consultation facilitated fidelity. We continually assessed clinicians' competence and monitored team functioning. *The control condition,* "community care" is psychosis treatment determined by clinician choice and service availability. Community care sites received no additional training or supervision except for guidance regarding subject recruitment, retention, and collection of research data.
Specialized Treatment Early in Psychosis (STEP)[8]	Key elements of STEP were: location within a Public (State mental health center)-Academic collaboration and thus sampling from the kinds of patients who would usually present to an urban community mental health center with the caveat that STEP was allowed to also admit individuals with commercial insurance, or those who lived outside the CMHCs traditional catchment or those who were 16 or 17yo (i.e. not just 18 and above). The STEP pragmatic RCT was specifically designed to be pragmatic in all 3 dimensions i.e. (i) sampling from patients who are close to naturalistic presenting populations; (ii) treating in a manner that would be feasible in a CMHC and (iii) measuring outcomes that were of relevance to patients/policymakers (work/school per dept of labor criteria) and at a frequency that was sustainable for such a service (i.e. we did not do SURF measures every month: this would constitute to my mind a kind of co-intervention). All of this comes with limitations of course, one of which, is that we do not have detailed utilization data (CMHC has no EMR and we did not ask patients to report on their use of services in STEP or TAU every month). We are preparing a cost paper though, that treats the delivery of the specialized interventions (CBT groups, MFG, team meetings) as 'fixed' costs that were invariant to patient utilization and making the best use of incomplete data from administrative sources on other variable costs. *Treatment as usual* included what patients were able to access in the community, based on their insurance coverage. TAU differed qualitatively (no TAU patient we queried received the specialized interventions like CBT, MFG etc) and quantitatively (of the shared components of Psychiatrist, clincian and visiting nurse visits, TAU received slightly less than STEP).
Integrated treatment to functional recovery, Study 1 (Valencia 12 Months)[9]	The integrated approach was composed of the following interventions: 1. Psychosocial Treatment. The design process of the treatment program included the identification of clinical and psychosocial problems of patients, as well as family members' needs and demands. All patients were receiving antipsychotic medication. In addition, various areas were identified where patients had difficulties that interfered with their community-functioning medication and symptom management, social and family problems. Therefore, learning certain skills was set as a goal, that is, medication compliance, acquiring knowledge about the illness, identifying warning signs of relapse, developing a relapse preventive plan, developing skills to manage social relations, and learning problem-solving skills for better family relations. Various therapeutic modalities were recommended as components of an integrated and comprehensive mental health system including antipsychotic medication, psychosocial treatment, psychoeducation, and family therapy. Psychosocial treatment included these four areas: (1) medication management, (2) symptom management, (3) social relations, and (4) family relations. All are described in a therapist's manual that includes the skills corresponding to each area, plus training strategies for each session. Two therapists taught patients skill acquisition using the "learning activities". The seven proposed learning activities were reduced to six, since video technology used in the

	United States has not yet been developed in Mexico. Learning activities included (1) introduction and explanation of skills to be learned in each session, (2) skill demonstration by therapists that included a question-and-answer segment for clarification of skills to be learned, (3) patient practice of skills using role playing and other techniques, (4) feedback allowing patients to identify resources needed to use skills in the real world, (5) practice skills in the community, and, (6) each session began with verification of skills registered in a learning checklist. A therapist evaluation form was used to verify that all treatment areas were conducted properly. Therapists' competency during treatment was assessed by a specially trained research assistant. Before treatment, competency levels had to be demonstrated with at least a 90 percent level of efficacy. Monitoring for maintenance of fidelity occurred throughout the study. Group sessions, six patients per group, were conducted weekly by two therapists with a time limit of 75 minutes during one year of treatment. 2. *Psychoeducation*. This intervention was mandatory for at least one relative per family who received information during ten multifamily group sessions about the illness, symptoms, medication management, side effects, compliance, keeping appointments, and recognition and management of warning signs of relapse. In addition, four sessions for each patient and his family were held oriented to problem solving and improving communication skills. Two family therapists were in charge of Psychoeducation and family sessions. 3. *Pharmacological Treatment*. Patients of both groups received medication management at the Schizophrenia Clinic of the National Institute of Psychiatry. Two clinical psychiatrists, who were blind to the two treatment conditions, gave patients 20-minute monthly consultations, registered attendance, controlled prescription of antipsychotic medication, and verified compliance with medication during one year of treatment. Professional participants in the treatment team included two psychiatrists for medication management, two clinical psychologists in charge of psychosocial treatment, and two family therapists for Psychoeducation and family sessions. Comparison: Medication only (monthly review)
Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	The *integrated treatment* can be defined as a comprehensive model including socials skills training, psychoeducation for relatives, family therapy and pharmacotherapy. 1. *Social skills training*: Social skills training focused on four areas: a) medication management, b) symptom management, c) social relations, and d) family relations. Learning certain skills was set as a goal that included: learning about the illness, compliance with medication, identifying warning signs of relapse, developing a relapse preventive plan, learning skills to manage social relations, and learning problem-solving skills for better family relations. A therapist´s manual describes the areas including the skills corresponding to each area, and the training strategies for each session (Valencia et al., 2001). Two therapists were in charge of teaching patients' skill acquisition using the "learning activities". Six learning activities were utilized: 1) introduction and explanation of skills to be learned in each session; 2) skill demonstration by therapists that included a question-and-answer segment for clarification of skills to be learned; 3) patient practice of skills using role playing and other techniques; 4) feedback allowing patients to identify resources needed to use skills in the real world; 5) practice skills in the community; and, 6) each session began with verification of skills registered in a learning check-list. Of the seven originally proposed learning activities, six were utilized excluding video technology as it is being used in the United States since this type of technology has not yet been developed in Mexico. As a substitute of video technology live demonstration of the learning skills by the therapists were carried out during sessions. A therapist evaluation form was used to verify that all treatment areas were conducted properly. Therapists´ competency during treatment was assessed by a specially trained research assistant. Before treatment, competency levels had to be demonstrated with at least a 90 percent level of efficacy. Monitoring for maintenance of fidelity occurred throughout the study. Group sessions, eight patients per group, were conducted weekly by two therapists with a time limit of 90 minutes during six-month of treatment. Goals of the interventions included: 1) training patients to acquire social skills; 2) improving psychosocial functioning, 3) preventing relapse and rehospitalization, 4) promoting treatment compliance, and 5) achieving functional outcome measured by symptomatic remission and psychosocial functioning. 2. *Psycho-education* Eight multi-family group sessions were held where relatives received information about schizophrenia, symptoms, medication management, side effects, compliance with medication, keeping appointments, and recognition and management of warning signs of relapse. As it was requested in the inclusion criteria, at least one relative per family had to participate, but if more relatives expressed their desire to participate, they were welcomed to psychoeducation and family sessions. Family therapy included four sessions for each patient and his family focused on problem solving and improving communication skills. Two family therapists were in charge of psychoeducation and family sessions. Integrated treatment included the following professionals: two psychiatrists for medication management, two clinical psychologists in charge of psychosocial treatment, and two family therapists for

	psycho-education and family sessions. *Standard treatment* consisted of the usual service provided to patients: pharmacological treatment that was provided at the Schizophrenia Clinic of the National Institute of Psychiatry. Patients of both groups under study attended 20-minute monthly consultations given by two clinical psychiatrists, who were blind to the two treatment conditions. In addition of controlling prescribed antipsychotic medication, the treating psychiatrists were in charge of registering attendance to consultations and verifying medication compliance with patients´ and their corresponding relatives during consultations.

Supplement 9: eTable 4**: Risk of Bias summary table**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (Symptom reduction, response)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other sources of bias	NUMBER OF LOW RISK RATINGS
COAST[1]	low	low	high	low	high	low	low	5
JCEP[2]	low	low	high	low	low	low	low	6
LEO[3]	low	low	high	low	low	low	high	5
OPUS[4]	low	low	high	high	low	low	low	5
OTP[5]	low	low	high	low	low	low	low	6
PIANO[6]	low	low	high	high	low	low	high	4
RAISE-ETP[7]	low	low	low	low	low	low	low	7
STEP[8]	low	low	high	high	high	low	low	4
Integrated treatment to functional recovery, Study1 (Valencia 12 Months)[9]	low	low	low	low	high	low	high	5
Integrated treatment to functional recovery, Study 2 (Valencia 6 Months)[10]	low	low	low	low	high	low	high	5

COAST: Croydon Outreach and Assertive Support Team Study; JCEP: The Jockey Club Early Psychosis Study; LEO: Lambeth Early Onset Study; OTP: Optimal Treatment Project Study; OPUS: Specialized assertive intervention; PIANO: Psychosis: early Intervention and Assessment of Needs and Outcome Study; RAISE-ETP: Recovery After an Initial Schizophrenia Episode-Early Treatment Program Study; STEP: Specialized Treatment Early in Psychosis Study

Supplement 10: eTable 5. **Risk of bias for single studies**

COAST (UK)[1]		
Selection bias		
Random sequence generation	Low risk	Quote: "Randomization was based on permuted blocks of size 8, and was carried out by an administrator who was independent of the trial using a computer programme" Comment: Probably done.
Allocation concealment	Low risk	Quote: "Concealed randomization procedure… by an administrator who was independent of the trial..." Comment: Probably done
Performance bias		
Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "Main rater was asked to guess the allocation of participants to COAST or TAU…was not able to do it…better than chance…so that she was effectively blind to intervention group while conducting the study…"". Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	High risk	Quote: "The main limitation of the study was poor follow-up of both individuals and carers, and the paucity of carers recruited, despite the focus of COAST on this part of their service. Despite consistent efforts, it was not possible to re-interview considerable numbers of clients" Comment: High risk
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other source of bias		
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
JCEP (Hong-Kong)[2]		
Selection bias		
Random sequence generation	Low risk	Quote: "Participants were randomly assigned to receive either 4 years of EI service, 2 years of EI service, or 4 years of standard care. The service has incorporated a randomized controlled trial" Comment: probably done
Allocation concealment	Low risk	Quote: "a randomization list was generate using the Stats-Direct software", "since a small block size may lead to guessing and thus reduce blinding, a large block size with random sequences between 6 and 12 without stratification was applied. During randomization, research staff called the Project Office; and patient was then assigned in sequence a unique Project ID and the treatment arm according to the randomization list. (…) The persons generating the randomization schedule and assigning the treatment arm were not involved with determining patient´s eligbility, treatment or assessment of outcomes": Comment: probably done
Performance bias		
Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "The outcome assessments are independently recorded by research assistants who are blinded to the treatment arm of the patients, and they are not involved in delivering intervention" Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been

		broken.
Attrition bias		
Incomplete outcome data addressed	Low risk	Quote: Only very few drop-outs, dataset very complete. Comment: Low risk
Reporting bias		
Selective reporting	Low risk	Quote: All pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
LEO (UK)[3]		
Selection bias		
Random sequence generation	Low risk	Quote: "The process of randomisation and allocation was carried out independently allocation was carried out independently of the research or clinical team by the trial of the research or clinical team by the trial statistician (G.D.), based in Manchester". Comment: Probably Done
Allocation concealment	Low risk	Quote: "Allocation was carried out independently of the research or clinical team by the trial of the research or clinical team by the trial statistician (G.D.), based in Manchester". "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" Comment: Probably Done
Performance bias		
Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "Group allocation remained concealed... two raters correctly guessed… of 60% (95% CI 52-63)". Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	Low risk	Quote: Drop-out rate of 3-8% Comment: Missing outcome data relatively balanced across intervention groups.
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	High risk	Quote: Endpoint data analysis only Comment: High risk
OPUS (Denmark)[4]		
Selection bias		
Random sequence generation	Low risk	Quote: "Patients were centrally randomized to the intensive early-intervention program or standard treatment…randomization was carried out through centralized telephone randomization…The allocation sequence was a computer-generated ratio of 1:1 in blocks of 6, and stratified for each of 5 center." Comment: probably done
Allocation concealment	Low risk	Quote: "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." Comment: probably done
Performance bias		
Blinding of	High	Quote: Blinding of participants and treatment providers not possible due to kind of intervention

participants and personnel	risk	Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	High risk	Quote: "Blinding of the assessors to treatment allocation would have been optimal, but allocation would have been optimal, but this was not judged to be possible in this this was not judged to be possible in this kind of trial." Comment: High risk
Attrition bias		
Incomplete outcome data addressed	Low risk	Quote: Percentage not finishing the study: 17% (OPUS) vs 29% (TAU). Comment: Missing data have been imputed using appropriate methods.
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
OTP (Norway)[5]		
Selection bias		
Random sequence generation	Low risk	Quote: "Patients were randomly allocated to IT or TAU using a sequence of sealed pre-numbered envelopes with group assignments according to random numbers provided by the International Optimal Treatment Project administration" Comment: Probably Done
Allocation concealment	Low risk	Quote: "sealed pre-numbered envelopes", "A secretary outside clinical services opened the envelopes" Comment: Probably Done
Performance bias		
Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	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" Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	Low risk	Quote: All participants were included in the assessments in the two-year intervention period Comment: Low risk
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias		
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
PIANO (Italy)[6]		
Selection bias		
Random sequence generation	Low risk	Quote: "cluster-randomized controlled trial", "stratified randomization of CMHCs" Comment: probably done
Allocation concealment	Low Risk	Quote: Cluster randomized Comment: Even though the trial used cluster randomization, participants or investigators enrolling participants could not influence the patient allocation and introduce selection bias, as - according to the Italian legislation – community services work for a specific catchment area and patients cannot choose between service providers.
Performance bias		

Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	High risk	Quote: "Patient, clinicians and raters could not be blinded" Comment: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding
Attrition bias		
Incomplete outcome data addressed	Low Risk	Quote: Percentage not finishing the study: 11-12%. "Service disengagement was assessed by interviewing patients who interrupted contact with services before study termination", "ITT approach used in the analyses" Comment: low risk
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	High risk	Quote: Endpoint data analysis only Comment: High risk
RAISE-ETP (US)[7]		
Selection bias		
Random sequence generation	Low risk	Quote: "Cluster randomization design", "Clinics were randomly assigned to the experimental intervention or standard care for FEP. No site withdrew after learning of their assignment" Comment: Even though no random sequence generation process was used on the patient level, random sequence allocation was applied on a clinic level after appropriate matching of clinics based on pertinent population characteristics, assigning clinics either to the intervention or Community Care.
Allocation concealment	Low risk	Quote: Cluster randomized Comment: Even though the trial used cluster randomization, participants or investigators enrolling participants could not influence the patient allocation and introduce selection bias, as sites were far apart from each other and patients received care in the respective center whether or not they agreed to participating in the research project.
Performance bias		
Blinding of participants and personnel	Low risk	Comment: Even though participants and treatment providers were not blinded to the kind of intervention, the outcomes are unlikely to have been influenced by performance bias, as assessments were performed by central and blinded assessors.
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "…Centralized assessors, who were blind to individual treatment assignments and the overall study design" Comment: Blinding of outcome assessment was ensured by use of centralized assessments via two-way video, and it is unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	Low risk	Quote: Percentage not finishing the study: 35% (RAISE-ETP) vs 54% (TAU). Comment: Missing data were imputed using appropriate methods ensuring analysis in the full intent-to-treat- population
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
STEP (US)[8]		
Selection bias		
Random sequence generation	Low risk	Quote: Eligible patients were randomly assigned to STEP or to treatment as usual by permuted and concealed random blocks between 2 and 5." Comment: Probably done

Allocation concealment	Low risk	Quote: "The research statistician independently generated the random sequence kept in sealed envelopes" Comment: Probably done
Performance bias		
Blinding of participants and personnel	High risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	High risk	Quote: "using assessors independent of the treatment team, we minimized measurement bias, but blinding them to the intervention arm was not feasible" Comment: High risk
Attrition bias		
Incomplete outcome data addressed	High risk	Quote: Percentage not finishing the study: 20% (STEP) vs 16% (TAU). Comment: Attrition bias due to amount of incomplete outcome data. Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. Missing outcome data not balanced across intervention groups.
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	Low risk	Comment: The study appears to be free of other sources of bias.
Integrated treatment to functional recovery, Study 1: Valencia 12 MONTHS (Mexico)[9]		
Selection bias		
Random sequence generation	Low risk	Quote: "Patients were randomly assigned" Comment: All patients recruited were assigned a number, that was written on a little piece of paper and folded so no one can see the corresponding number. All numbers were introduced in a bowl and from that bowl numbers were taken out, one number for the experimental group and the next number for the control group until all patients were allocated to the two groups.
Allocation concealment	Low risk	Comment: There is a low risk of bias if participants or investigators enrolling participants could possibly foresee assignments (see information above)
Performance bias		
Blinding of participants and personnel	Low risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: Even though participants and treatment providers were not blinded to the kind of intervention, the outcomes are unlikely to have been influenced by performance bias, as raters were blind to the research project and the interventions provided.
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "Rater (…) were blind to which study group a patient belonged to (…). Raters did not participate in the treatment team and had no knowledge of the research project." Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	High risk	Quote: Percentage not finishing the study: 11% (integrated care) vs 36% (TAU) Comment: Attrition bias due to amount of incomplete outcome data. Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. Missing outcome data not balanced across intervention groups.
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	High risk	Quote: Observed cases analysis only Comment: High risk
Integrated treatment to functional recovery, Study 2: Valencia 6 MONTHS (Mexico)[10]		
Selection bias		

Random sequence generation	Low risk	Quote: "Patients were randomly assigned" Comment: All patients recruited were assigned a number, that was written on a little piece of paper and folded so no one can see the corresponding number. All numbers were introduced in a bowl and from that bowl numbers were taken out, one number for the experimental group and the next number for the control group until all patients were allocated to the two groups.
Allocation concealment	Low risk	Comment: There is a low risk of bias if participants or investigators enrolling participants could possibly foresee assignments (see information above)
Performance bias		
Blinding of participants and personnel	Low risk	Quote: Blinding of participants and treatment providers not possible due to kind of intervention Comment: Even though participants and treatment providers were not blinded to the kind of intervention, the outcomes are unlikely to have been influenced by performance bias, as raters were blind to the research project and the interventions provided.
Detection bias		
Blinding of outcome assessment (Symptom severity, relapse)	Low risk	Quote: "Independent interviewers that were blind to the two treatment conditions completed the assessments." Comment: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Attrition bias		
Incomplete outcome data addressed	High risk	Quote: Drop-out rate of 10% (integrated care) vs 20% (TAU) Comment: Attrition bias due to amount of incomplete outcome data. Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. Missing outcome data not balanced across intervention groups.
Reporting bias		
Selective reporting	Low risk	Quote: Pre-specified outcomes are reported. Comment: Low risk
Other sources of bias	High risk	Quote: Observed cases analysis only Comment: High risk

COAST: Croydon Outreach and Assertive Support Team Study; JCEP: The Jockey Club Early Psychosis Study; LEO: Lambeth Early Onset Study; OTP: Optimal Treatment Project Study; OPUS: Specialized assertive intervention; PIANO: Psychosis: early Intervention and Assessment of Needs and Outcome Study; RAISE-ETP: Recovery After an Initial Schizophrenia Episode-Early Treatment Program Study; STEP: Specialized Treatment Early in Psychosis Study

Supplement 11: eTable 6: **Co-Primary Outcomes – Overall results, Subgroup Analyses and Meta-Regression**

		ALL-CAUSE TREATMENT DISCONTINUATION								HOSPITALIZATION [a]							
		N	n	RR	95% CI		Result:	Heterogeneity		N	n	RR	95% CI		Result:	Heterogeneity	
					lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2
All studies		**10**	**2173**	**0.701**	**0.613**	**0.802**	**0.000**	0.434	0.4	**10**	**2105**	**0.740**	**0.609**	**0.900**	**0.003**	0.047	47.5
DATA ANALYSIS	ITT	**6**	**1377**	**0.704**	**0.593**	**0.837**	**0.000**	0.396	3.1	**6**	**1376**	**0.772**	**0.606**	**0.984**	**0.036**	0.340	11.8
	Endpoint	4	796	0.730	0.525	1.015	0.062	0.286	20.7	**4**	**729**	**0.659**	**0.459**	**0.947**	**0.024**	0.021	69.3
REGION	Europe	**5**	**1244**	**0.760**	**0.623**	**0.926**	**0.006**	0.173	37.2	5	1223	0.819	0.648	1.035	0.094	0.369	6.6
	Rest of the world	3	408	0.574	0.312	1.054	0.073	0.669	0.0	**3**	**361**	**0.444**	**0.261**	**0.756**	**0.003**	0.197	38.5
	United states	**2**	**521**	**0.657**	**0.509**	**0.849**	**0.001**	0.499	0.0	2	521	0.779	0.549	1.106	0.163	0.076	68.3
BLINDED OUTCOME ASSESSMENT	No	**3**	**1108**	**0.737**	**0.573**	**0.948**	**0.017**	0.184	40.9	3	1096	0.839	0.608	1.157	0.285	0.130	50.9
	Yes	**7**	**1065**	**0.696**	**0.570**	**0.851**	**0.000**	0.470	0.0	**7**	**1009**	**0.652**	**0.493**	**0.864**	**0.003**	0.107	42.6
SCALABLE FIDELITY MONITORING	No	4	520	0.844	0.648	1.099	0.207	0.572	0.0	**4**	**511**	**0.621**	**0.451**	**0.856**	**0.004**	0.876	0.0
	Yes	**6**	**1653**	**0.658**	**0.563**	**0.768**	**0.000**	0.480	0.0	6	1594	0.828	0.675	1.015	0.069	0.045	56.0
FIDELITY OUTCOMES REPORTED	No	**7**	**778**	**0.775**	**0.608**	**0.988**	**0.040**	0.619	0.0	**7**	**722**	**0.575**	**0.452**	**0.732**	**0.000**	0.544	0.0
	Yes	3	1395	0.672	0.570	0.790	0.000	0.161	45.2	3	1383	0.906	0.816	1.005	0.061	0.733	0.0
FAMILY THERAPY	No	**3**	**748**	**0.643**	**0.524**	**0.788**	**0.000**	0.812	0.0	3	740	0.785	0.538	1.146	0.210	0.417	0.0
	Yes	**7**	**1425**	**0.748**	**0.627**	**0.893**	**0.001**	0.285	19.0	**7**	**1365**	**0.678**	**0.509**	**0.903**	**0.008**	0.018	60.9
CRISIS RESPONSE TEAM	No	**6**	**1317**	**0.684**	**0.559**	**0.836**	**0.000**	0.466	0.0	**6**	**1250**	**0.688**	**0.511**	**0.926**	**0.014**	0.018	63.3
	Yes	**4**	**856**	**0.744**	**0.592**	**0.935**	**0.011**	0.252	26.7	4	855	0.757	0.530	1.081	0.126	0.497	0.0
SOCIAL SKILLS TRAINING	No	**5**	**1168**	**0.744**	**0.631**	**0.877**	**0.000**	0.159	39.3	5	1147	0.764	0.559	1.045	0.092	0.177	36.6
	Yes	**5**	**1005**	**0.627**	**0.499**	**0.787**	**0.000**	0.906	0.0	**5**	**958**	**0.647**	**0.453**	**0.924**	**0.017**	0.031	62.4
VOCATIONAL INTERVENTION	No	**5**	**1249**	**0.683**	**0.535**	**0.871**	**0.002**	0.362	7.8	5	1190	0.736	0.534	1.014	0.061	0.024	64.3
	Yes	**5**	**924**	**0.730**	**0.598**	**0.892**	**0.002**	0.339	11.7	**5**	**915**	**0.704**	**0.517**	**0.959**	**0.026**	0.327	13.6
METAREGRESSION																	
Covariate		N	n	Coefficient	95% CI		Result:	Heterogeneity		N	n	Coefficient	95% CI		Result:	Heterogeneity	
					lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2
Sample Size		10	2173	0.000	-0.001	0.000	0.272	0.434	0.5	**10**	**2105**	**0.001**	**0.000**	**0.002**	**0.002**	0.047	47.5
Number of sites		10	2173	-0.004	-0.013	0.005	0.336	0.434	0.5	10	2105	0.011	-0.007	0.029	0.241	0.047	47.5
Duration of Intervention		10	2173	-0.022	-0.043	-0.001	0.036	0.434	0.5	10	2105	0.023	-0.005	0.051	0.113	0.047	47.5
Risk of Bias		10	2173	-0.089	-0.215	0.036	0.163	0.434	0.5	10	2105	0.060	-0.161	0.281	0.594	0.047	47.5
Number of Treatment Components		10	2173	0.132	-0.050	0.315	0.154	0.434	0.5	10	2105	-0.048	-0.326	0.231	0.737	0.047	47.5
Ratio Visits EIS / TAU		4	858	-0.049	-0.358	0.259	0.754	0.902	0.0	4	850	0.217	-0.015	0.448	0.066	0.159	42.1
% Schizophrenia		10	2173	-0.312	-1.101	0.476	0.438	0.434	0.5	10	2105	-0.651	-1.522	0.219	0.143	0.047	47.5
GAF at baseline		7	1510	-0.001	-0.071	0.069	0.975	0.586	0.0	7	1443	0.011	-0.068	0.090	0.791	0.018	61.0
% patient at school/work at baseline		8	2067	0.014	-0.011	0.038	0.283	0.652	0.0	8	2067	-0.007	-0.032	0.018	0.582	0.030	55.0
PANSS at baseline		8	1576	-0.027	-0.060	0.006	0.103	0.327	13.2	8	1508	-0.014	-0.044	0.016	0.350	0.046	51.2
PANSS/converted BPRS at baseline		9	1626	-0.028	-0.061	0.005	0.093	0.400	4.2	9	1558	-0.013	-0.040	0.015	0.369	0.070	44.7
PANSS-P at baseline		8	1576	-0.094	-0.209	0.021	0.109	0.327	13.2	8	1508	-0.033	-0.131	0.064	0.502	0.046	51.2
PANSS-N at baseline		**8**	**1576**	**-0.080**	**-0.151**	**-0.008**	**0.029**	0.327	13.2	8	1508	-0.048	-0.139	0.043	0.297	0.046	51.2
Number of prior hospitalizations		7	1517	-0.390	-0.907	0.127	0.139	0.555	0.0	7	1450	-0.685	-1.409	0.039	0.064	0.331	56.2
Mean age		10	2173	0.048	-0.005	0.100	0.075	0.434	0.45	10	2105	0.011	-0.042	0.064	0.687	0.047	47.5
% Male		10	2173	0.206	-1.717	2.129	0.834	0.434	0.45	10	2105	-1.250	-3.347	0.846	0.242	0.047	47.5
Mean duration of prior AP treatment		4	1192	-0.007	-0.030	0.015	0.522	0.282	21.5	4	1172	-0.011	-0.025	0.003	0.120	0.424	0.0
Mean DUP		5	1309	-0.001	-0.004	0.001	0.260	0.401	0.9	5	1289	0.001	-0.002	0.005	0.372	0.234	28.2
Median DUP		5	1309	-0.005	-0.011	0.002	0.152	0.401	0.9	5	1289	0.003	-0.006	0.012	0.499	0.234	28.2
Overall attrition		-	-	-	-	-	-	-	-	10	2105	0.003	-0.017	0.017	0.679	0.047	47.5
Between-group attrition difference		-	-	-	-	-	-	-	-	10	2105	0.007	-0-022	0.035	0.655	0.047	47.5

[a] One study[1] did not clearly specify whether the hospitalizations represented individual patients (assumed by us) or the sum of all admissions

RRs below 1 indicate that a specific categorical outcome occurred less frequently in EIS
BPRS=brief psychiatric rating scale; CI=confidence interval; DUP=duration of untreated psychosis; GAF=Global Assessment of Functioning; ITT=intent to treat; N=number of studies; n=number of patients; OC=observed cases; PANSS=positive and negative syndrome scale; PANSS-N=PANSS negative subscale; PANSS-P=PANSS positive subscale; RR=risk ratio

Supplement 12: eTable 7**: Key secondary - Overall results, Subgroup Analyses and Meta-Regression**

		TOTAL SYMPTOM IMPROVEMENT								FUNCTIONING [a]								INVOLVEMENT IN SCHOOL AND WORK							
		N	n	SMD	95% CI		Result:	Heterogeneity		N	n	SMD	95% CI		Result:	Heterogeneity		N	n	RR	95% CI		Result:	Heterogeneity	
					lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2
All studies		**8**	**1179**	**-0.322**	**-0.474**	**-0.170**	**0.000**	0.175	31.7	**7**	**1005**	**0.210**	**0.085**	**0.336**	**0.001**	0.590	0.0	**6**	**1743**	**1.126**	**1.026**	**1.235**	**0.012**	0.659	0.0
DATA ANALYSIS	ITT	**4**	**535**	**-0.274**	**-0.510**	**-0.039**	**0.022**	0.331	12.3	5	515	0.112	-0.062	0.285	0.207	0.766	0.0	4	1174	1.125	0.987	1.282	0.077	0.569	0.0
	Endpoint	**4**	**644**	**-0.381**	**-0.611**	**-0.150**	**0.001**	0.098	52.4	**2**	**490**	**0.318**	**0.136**	**0.500**	**0.001**	0.641	0.0	2	569	1.126	0.988	1.284	0.075	0.264	19.9
REGION	Europe	3	531	-0.265	-0.572	0.042	0.090	0.504	0.0	**5**	**747**	**0.269**	**0.123**	**0.416**	**0.000**	0.711	0.0	3	1060	1.111	0.990	1.247	0.074	0.488	0.0
	Rest of the world	**3**	**353**	**-0.406**	**-0.720**	**-0.092**	**0.011**	0.016	75.9	1	192	0.020	-0.263	0.303	0.889	1.000	0.0	1	192	1.205	0.908	1.598	0.197	1.000	0.0
	United states	2	295	-0.355	-0.727	0.017	0.062	0.774	0.0	1	66	0.115	-0.369	0.599	0.641	1.000	0.0	**2**	**491**	**1.130**	**0.941**	**1.358**	**0.191**	0.212	35.8
BLINDED OUTCOME ASSESSMENT	No	2	459	-0.300	-0.615	0.015	0.062	0.575	0.0	**3**	**650**	**0.220**	**0.063**	**0.376**	**0.006**	0.518	0.0	3	1022	1.114	0.993	1.249	0.065	0.472	0.0
	Yes	**6**	**720**	**-0.346**	**-0.551**	**-0.141**	**0.001**	0.080	49.2	4	355	0.192	-0.018	0.402	0.072	0.349	8.8	3	721	1.148	0.981	1.343	0.084	0.434	0.0
SCALABLE FIDELITY MONITORING	No	3	352	-0.140	-0.367	0.087	0.228	0.468	0.0	4	372	0.158	-0.046	0.363	0.129	0.394	0.0	**3**	**404**	**1.291**	**1.071**	**1.556**	**0.007**	0.813	0.0
	Yes	**5**	**827**	**-0.391**	**-0.550**	**-0.232**	**0.000**	0.257	24.7	**3**	**633**	**0.241**	**0.082**	**0.400**	**0.003**	0.531	0.0	3	1339	1.077	0.968	1.198	0.172	0.937	0.0
FIDELITY OUTCOMES REPORTED	No	**6**	**561**	**-0.358**	**-0.574**	**-0.143**	**0.001**	0.076	49.9	5	421	0.180	-0.012	0.373	0.067	0.498	0.0	**3**	**404**	**1.291**	**1.071**	**1.556**	**0.007**	0.813	0.0
	Yes	**2**	**618**	**-0.286**	**-0.559**	**-0.014**	**0.039**	0.688	0.0	**2**	**584**	**0.232**	**0.067**	**0.398**	**0.006**	0.291	10.2	3	1339	1.077	0.968	1.198	0.172	0.937	0.0
FAMILY THERAPY	No	3	511	-0.176	-0.377	0.025	0.086	0.375	0.0	2	290	0.147	-0.084	0.378	0.213	0.126	57.2	3	721	1.148	0.981	1.343	0.084	0.434	0.0
	Yes	**5**	**668**	**-0.422**	**-0.604**	**-0.240**	**0.000**	0.272	22.3	**5**	**715**	**0.236**	**0.087**	**0.386**	**0.002**	0.753	0.0	3	1022	1.114	0.993	1.249	0.065	0.472	0.0
CRISIS RESPONSE TEAM	No	**6**	**939**	**-0.364**	**-0.535**	**-0.192**	**0.000**	0.270	21.7	**3**	**556**	**0.293**	**0.123**	**0.463**	**0.001**	0.667	0.0	**4**	**1060**	**1.128**	**1.014**	**1.255**	**0.027**	0.422	0.0
	Yes	2	240	-0.176	-0.491	0.139	0.274	0.148	52.2	4	449	0.111	-0.075	0.297	0.241	0.608	0.0	2	683	1.120	0.930	1.348	0.233	0.501	0.0
SOCIAL SKILLS TRAINING	No	**4**	**778**	**-0.271**	**-0.485**	**-0.056**	**0.013**	0.782	0.0	**4**	**572**	**0.300**	**0.133**	**0.468**	**0.000**	0.784	0.0	**4**	**1060**	**1.128**	**1.014**	**1.255**	**0.027**	0.422	0.0
	Yes	**4**	**401**	**-0.409**	**-0.663**	**-0.155**	**0.002**	0.033	65.6	3	433	0.095	-0.094	0.284	0.322	0.593	0.0	2	683	1.120	0.930	1.348	0.233	0.501	0.0
VOCATIONAL INTERVENTION	No	**4**	**600**	**-0.439**	**-0.649**	**-0.229**	**0.000**	0.161	41.7	**3**	**633**	**0.241**	**0.082**	**0.400**	**0.003**	0.531	0.0	2	935	1.086	0.961	1.227	0.184	0.819	0.0
	Yes	**4**	**579**	**-0.208**	**-0.407**	**-0.008**	**0.041**	0.440	0.0	4	372	0.158	-0.046	0.363	0.129	0.394	0.0	**4**	**808**	**1.182**	**1.025**	**1.363**	**0.021**	0.489	0.0
METAREGRESSION																									
Covariate		N	n	Coeffic ient	95% CI		Result:	Heterogeneity		N	n	Coeffic ient	95% CI		Result:	Heterogeneity		N	n	Coeffic ient	95% CI		Result:	Heterogeneity	
					lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2				lower limit	upper limit	p-value	p-Value	I2
Sample Size		8	1179	0.001	-0.001	0.002	0.355	0.175	31.7	7	1005	0.000	-0.001	0.001	0.907	0.590	0.0	6	1743	-0.001	-0.001	0.000	0.101	0.659	0.0
Number of sites		8	1179	0.001	-0.013	0.015	0.926	0.175	31.7	7	1005	0.033	-0.036	0.102	0.343	0.590	0.0	6	1743	-0.003	-0.011	0.004	0.393	0.659	0.0
Duration of Intervention		8	1179	0.014	-0.008	0.035	0.205	0.175	31.7	7	1005	-0.013	-0.031	0.006	0.173	0.590	0.0	6	1743	-0.001	-0.014	0.012	0.859	0.659	0.0
Risk of Bias		8	1179	0.022	-0.139	0.183	0.789	0.175	31.7	7	1005	-0.088	-0.243	0.068	0.271	0.590	0.0	6	1743	-0.015	-0.953	0.065	0.712	0.659	0.0
Number of Treatment Components		8	1179	0.084	-0.100	0.267	0.371	0.175	31.7	7	1005	-0.111	-0.262	0.040	0.149	0.590	0.0	6	1743	0.043	-0.093	0.179	0.537	0.659	0.0
Ratio Visits SCS / TAU		3	-	-	-	-	-	-	-	4	690	-0.088	-0.347	0.171	0.506	0.623	0.0	3	-	-	-	-	-	-	-
% Schizophrenia		**8**	**1179**	**-0.532**	**-0.955**	**-0.109**	**0.014**	0.175	31.7	7	1005	0.208	-0.356	0.771	0.470	0.590	0.0	6	1743	-0.080	-0.596	0.437	0.762	0.659	0.0

GAF at baseline	6	760	0.001	-0.057	0.058	0.983	0.240	25.9	5	1082	0.025	-0.019	0.069	0.258	0.711	0.0	4	1147	-0.015	-0.051	0.022	0.429	0.455	0.0
% patient at school	7	1520	0.011	-0.001	0.026	0.185	0.143	37.5	5	1455	-0.009	-0.022	0.005	0.221	0.418	0.0	6	1743	0.007	-0.005	0.018	0.261	0.659	0.0
PANSS at baseline	**7**	**1131**	**-0.013**	**-0.023**	**-0.003**	**0.010**	0.143	37.5	5	815	0.011	-0.002	0.025	0.096	0.425	0.0	5	1252	-0.003	-0.015	0.008	0.548	0.559	0.0
PANSS/ converted BPRS at baseline	**8**	**1179**	**-0.013**	**-0.023**	**-0.004**	**0.008**	0.175	31.7	6	864	0.011	-0.002	0.024	0.088	0.545	0.0	5	1252	-0.003	-0.015	0.008	0.548	0.559	0.0
PANSS-P at baseline	**7**	**1131**	**-0.038**	**-0.072**	**-0.003**	**0.031**	0.143	37.5	5	815	0.029	-0.011	0.069	0.149	0.425	0.0	5	1252	0.000	-0.034	0.033	0.979	0.559	0.0
PANSS-N at baseline	**7**	**1131**	**-0.043**	**-0.074**	**-0.012**	**0.007**	0.143	37.5	5	815	0.043	-0.011	0.096	0.115	0.425	0.0	5	1252	-0.011	-0.047	0.024	0.532	0.559	0.0
Number of prior hospitalizations	7	1131	-0.297	-0.605	0.010	0.058	0.143	37.5	4	799	-0.355	-0.811	0.102	0.128	0.329	12.7	5	1252	0.049	-0.220	0.317	0.722	0.559	0.0
Mean age	**8**	**1179**	**0.023**	**0.001**	**0.046**	**0.043**	0.175	31.7	7	1005	-0.014	-0.040	0.013	0.310	0.590	0.0	6	1743	0.001	-0.019	0.022	0.898	0.659	0.0
% Male	**8**	**1179**	**-1.120**	**-2.152**	**-0.089**	**0.033**	0.175	31.7	7	1005	0.760	-0.546	2.066	0.254	0.590	0.0	6	1743	0.102	-0.854	1.059	0.834	0.659	0.0
Mean duration of prior AP treatment	4	902	0.006	-0.006	0.018	0.312	0.518	0.0	3	-	-	-	-	-	-	-	4	1165	0.006	-0.004	0.016	0.226	0.601	0.0
Mean DUP	5	970	-0.001	-0.003	0.001	0.513	0.585	0.0	4	799	-0.006	-0.014	0.001	0.102	0.329	12.7	5	1252	-0.001	-0.002	0.001	0.366	0.559	0.0
Median DUP	5	970	-0.002	-0.007	0.003	0.470	0.585	0.0	4	799	-0.008	-0.075	0.060	0.828	0.329	12.7	5	1252	-0.001	-0.005	0.003	0.499	0.559	0.0
Overall attrition	8	1179	-0.001	-0.014	0.012	0.857	0.175	31.7	7	1005	0.003	-0.007	0.014	0.520	0.590	0.0	6	1743	-0.001	-0.008	0.006	0.718	0.660	0.0
Between-group attrition difference	8	1179	-0.009	-0.030	0.012	0.392	0.175	31.7	7	1005	-0.000	-0.19	0.018	0.989	0.590	0.0	6	1743	-0.002	-0.013	0.009	0.770	0.659	0.0

[a] Outcomes of 2 studies[9,10] were excluded from the analysis for being outliers with effect sizes of >2.4 favoring EIS

Negative SMD favored EIS when smaller values are better, positive SMD favored EIS when larger values are better (functioning, QoL); RRs below 1 indicate that a specific categorical outcome occurred less frequently in EIS

BPRS=brief psychiatric rating scale; CI=confidence interval; DUP=duration of untreated psychosis; GAF=Global Assessment of Functioning; ITT=intent to treat; N=number of studies; n=number of patients; OC=observed cases; PANSS=positive and negative syndrome scale; PANSS-N=PANSS negative subscale; PANSS-P=PANSS positive subscale; RR=risk ratio; SMD=standardized mean difference

Supplement 13: eTable 8**: Sensitivity subgroup-analysis (excluding two studies from Mexico)**

	ALL STUDIES								**SENSITIVITY ANALYSIS "WESTERN WORLD"**							
	N	n	SMD/ RR	95% CI		Result: p-value	Heterogeneity		N	n	SMD/ RR	95% CI		Result: p-value	Heterogeneity	
				lower limit	upper limit		p-Value	I2				lower limit	upper limit		p-Value	I2
TREATMENT DISCONTINUATION	**10**	**2173**	**0.701**	**0.613**	**0.802**	**0.000**	0.434	0.4	**8**	**1965**	**0.723**	**0.618**	**0.846**	**0.000**	0.330	12.8
ALL-CAUSE HOSPITALIZATION [a]	**10**	**2105**	**0.740**	**0.609**	**0.900**	**0.003**	0.047	47.5	**8**	**1944**	**0.841**	**0.743**	**0.953**	**0.007**	0.341	11.4
TOTAL SYMPTOM IMPROVEMENT	**8**	**1179**	**-0.322**	**-0.474**	**-0.170**	**0.000**	0.175	31.7	**6**	**1018**	**-0.240**	**-0.366**	**-0.114**	**0.000**	0.569	0.0
FUNCTIONING [b]	**7**	**1005**	**0.210**	**0.085**	**0.336**	**0.001**	0.590	0.0	**7**	**1005**	**0.210**	**0.085**	**0.336**	**0.001**	0.590	0.0
INVOLVEMENT IN SCHOOL AND WORK	**6**	**1743**	**1.126**	**1.026**	**1.235**	**0.012**	0.659	0.0	**6**	**1743**	**1.126**	**1.026**	**1.235**	**0.012**	0.659	0.0
POSITIVE SYMPTOM SEVERITY	**10**	**1532**	**-0.215**	**-0.318**	**-0.113**	**0.000**	0.433	0.5	**8**	**1371**	**-0.181**	**-0.289**	**-0.073**	**0.001**	0.640	0.0
NEGATIVE SYMPTOM SEVERITY	**10**	**1532**	**-0.280**	**-0.424**	**-0.137**	**0.000**	0.102	38.4	**8**	**1371**	**-0.209**	**-0.317**	**-0.100**	**0.000**	0.624	0.0
GENERAL SYMPTOM SEVERITY	**8**	**1118**	**-0.297**	**-0.468**	**-0.127**	**0.001**	0.111	40.2	**6**	**957**	**-0.211**	**-0.343**	**-0.079**	**0.002**	0.404	1.9
DEPRESSIVE SYMPTOM SEVERITY	**5**	**874**	**-0.193**	**-0.351**	**-0.034**	**0.017**	0.301	17.9	**5**	**874**	**-0.193**	**-0.351**	**-0.034**	**0.017**	0.301	17.9
REMISSION	**7**	**1229**	**1.291**	**1.074**	**1.552**	**0.007**	0.004	68.9	**5**	**1054**	**1.129**	**0.976**	**1.306**	**0.103**	0.197	33.6
RECOVERY	**3**	**640**	**1.243**	**1.032**	**1.498**	**0.022**	0.689	0.0	**3**	**640**	**1.243**	**1.032**	**1.498**	**0.022**	0.689	0.0
RELAPSE	**7**	**1275**	**0.706**	**0.534**	**0.933**	**0.014**	0.143	37.4	**5**	**1108**	**0.809**	**0.668**	**0.979**	**0.029**	0.783	0.0
MEAN NUMBER OF HOSPITALIZATIONS	**8**	**1412**	**-0.170**	**-0.312**	**-0.029**	**0.018**	0.157	35.5	**8**	**1412**	**-0.170**	**-0.312**	**-0.029**	**0.018**	0.157	35.5
DURATION OF HOSPITALIZATION	**6**	**1107**	**-0.167**	**-0.285**	**-0.049**	**0.006**	0.470	0.0	**6**	**1107**	**-0.167**	**-0.285**	**-0.049**	**0.006**	0.470	0.0
QUALITY OF LIFE	**4**	**505**	**0.230**	**0.004**	**0.456**	**0.046**	0.208	34.1	**4**	**505**	**0.230**	**0.004**	**0.456**	**0.046**	0.208	34.1

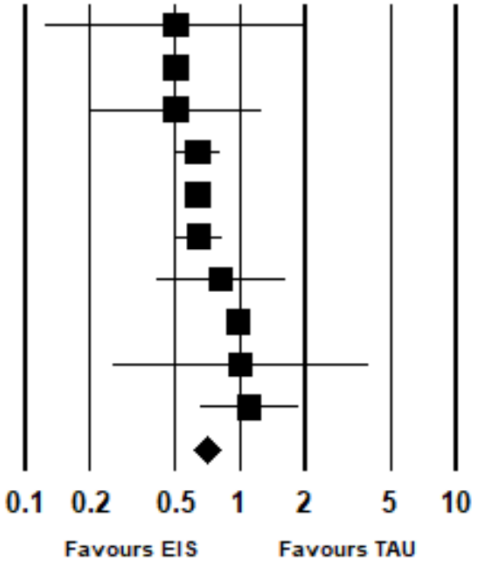
[a] One study[7] did not clearly specify whether the hospitalizations represented individual patients (assumed by us) or the sum of all admissions
[b] Outcomes of 2 studies[9,10] were excluded from the analysis for being outliers with effect sizes of >2.4 favoring EIS
Negative SMD favored EIS when smaller values are better, positive SMD favored EIS when larger values are better (functioning, QoL); RRs below 1 indicate that a specific categorical outcome occurred less frequently in EIS
CI=confidence interval; N=number of studies; n=number of patients; RR=risk ratio

Supplement 14: eFigure 1. **Forest Plot: All-cause treatment discontinuation**

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
OTP (5)	0.500	0.125	1.999	-0.980	0.327
Valencia 12M (9)	0.500	0.186	1.344	-1.374	0.169
Valencia 6M (10)	0.500	0.201	1.245	-1.489	0.136
RAISE-ETP (7)	0.636	0.507	0.798	-3.902	0.000
LEO (3)	0.638	0.391	1.041	-1.800	0.072
OPUS (4)	0.641	0.499	0.823	-3.490	0.000
STEP (8)	0.814	0.412	1.608	-0.592	0.554
COAST (1)	0.984	0.683	1.420	-0.084	0.933
JCEP (2)	1.000	0.257	3.888	0.000	1.000
PIANO (6)	1.098	0.646	1.868	0.346	0.729
	0.701	0.613	0.802	-5.170	0.000

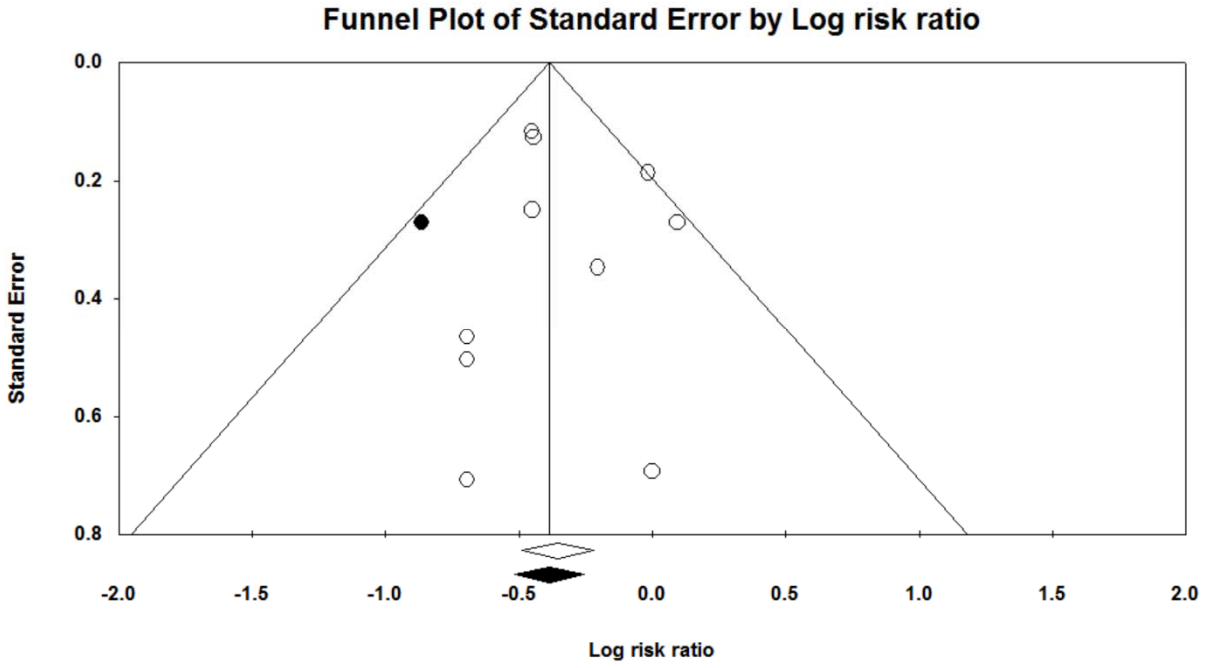
Statistics for each study

Risk ratio and 95% CI



Meta Analysis

Supplement 15: eFigure 2. **Funnel Plot: All-cause treatment discontinuation**



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.70105	0.61336	0.80126	0.70147	0.61324	0.80239	9.04026
Adjusted values	1	0.68010	0.59745	0.77420	0.68635	0.58443	0.80603	12.36572

Classic fail-safe N

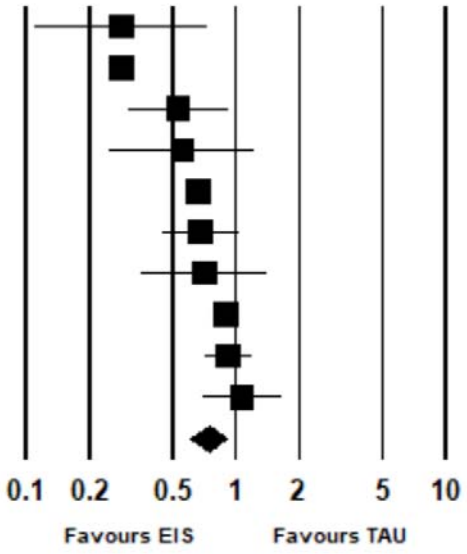
Z-value for observed studies	-4.22637
P-value for observed studies	0.00002
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	10.00000
Number of missing studies that would bring p-value to > alpha	37.00000

Egger's regression intercept

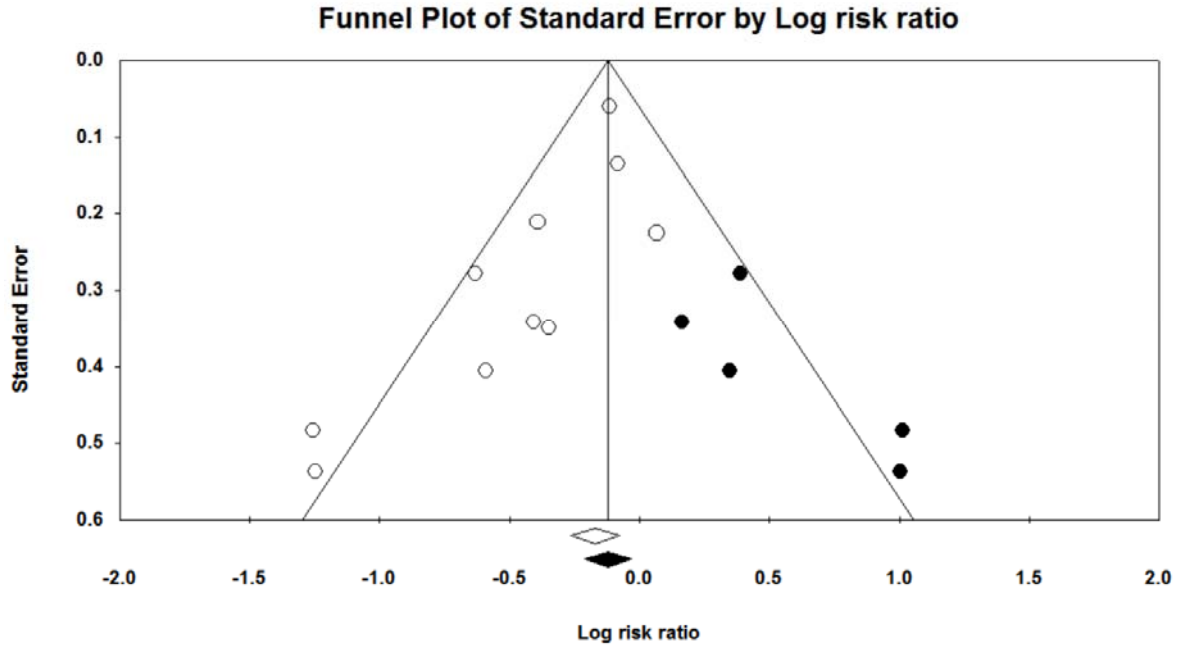
Intercept	0.22413
Standard error	0.63150
95% lower limit (2-tailed)	-1.23210
95% upper limit (2-tailed)	1.68037
t-value	0.35492
df	8.00000
P-value (1-tailed)	0.36591
P-value (2-tailed)	0.73182

Supplement 16: eFigure 3. **Forest Plot: Hospitalization**

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Valencia 6M (10)	0.285	0.111	0.734	-2.599	0.009
Valencia 12M (9)	0.287	0.100	0.823	-2.322	0.020
STEP (8)	0.532	0.309	0.917	-2.271	0.023
COAST (1)	0.554	0.250	1.227	-1.455	0.146
OTP (5)	0.667	0.341	1.302	-1.187	0.235
LEO (3)	0.677	0.448	1.023	-1.854	0.064
JCEP (2)	0.706	0.356	1.400	-0.997	0.319
OPUS (4)	0.892	0.794	1.003	-1.912	0.056
RAISE-ETP (7)	0.921	0.707	1.198	-0.615	0.539
PIANO (6)	1.070	0.687	1.664	0.298	0.766
Meta Analysis	0.740	0.609	0.900	-3.018	0.003



Supplement 17: eFigure 4. **Funnel Plot: Hospitalization**



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.84342	0.76669	0.92782	0.74047	0.60921	0.90002	17.13961
Adjusted values	5	0.88568	0.80814	0.97066	0.87200	0.71052	1.07017	33.44744

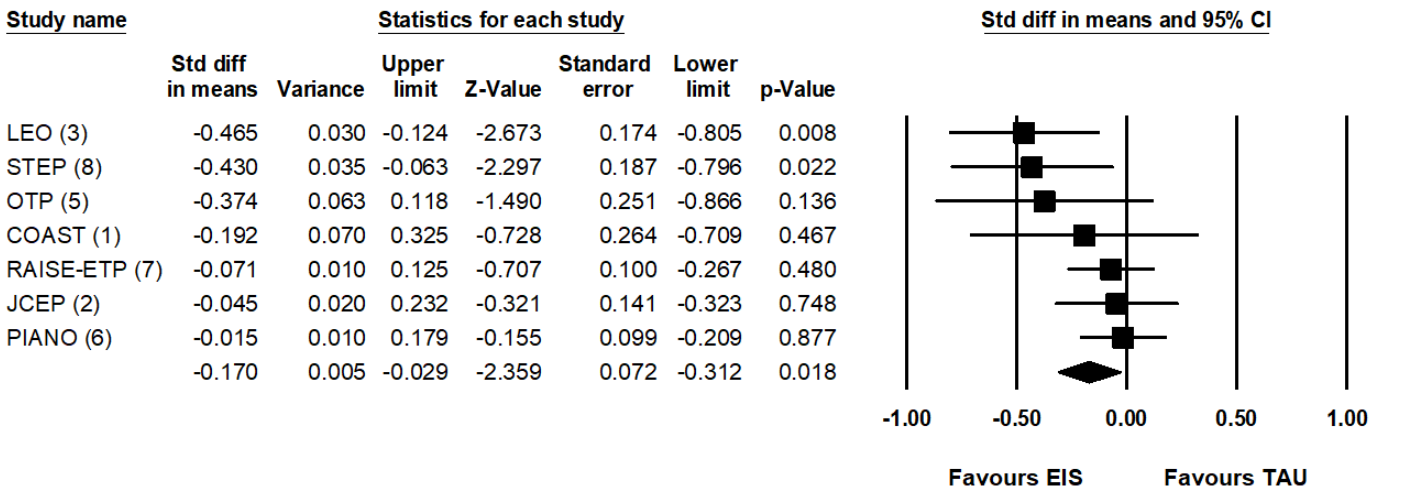
Classic fail-safe N

Z-value for observed studies	-4.71612
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	10.00000
Number of missing studies that would bring p-value to > alpha	48.00000

Egger's regression intercept

Intercept	-1.53020
Standard error	0.45674
95% lower limit (2-tailed)	-2.58344
95% upper limit (2-tailed)	-0.47697
t-value	3.35029
df	8.00000
P-value (1-tailed)	0.00504
P-value (2-tailed)	0.01008

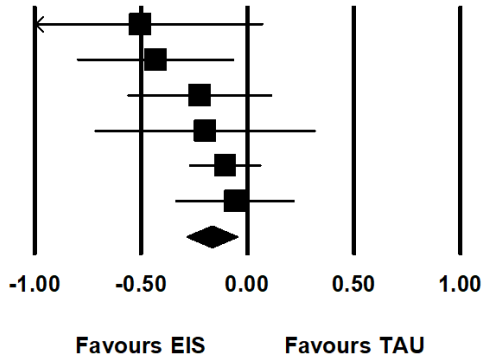
Supplement 18: eFigure 5. **Forest Plot: Mean number of hospital admissions**



Meta Analysis

Supplement 19: eFigure 6. **Forest Plot: Hospital bed days**

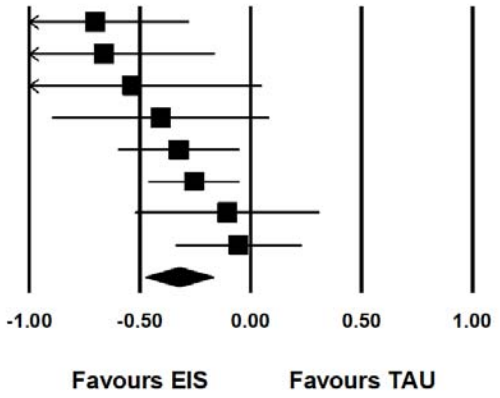
Study name	Std diff in means	Variance	Upper limit	Z-Value	Standard error	Lower limit	p-Value
OTP (5)	-0.504	0.086	0.071	-1.719	0.293	-1.078	0.086
STEP (8)	-0.432	0.035	-0.065	-2.308	0.187	-0.799	0.021
LEO (3)	-0.224	0.030	0.113	-1.304	0.172	-0.562	0.192
COAST (1)	-0.199	0.070	0.319	-0.752	0.264	-0.716	0.452
OPUS (4)	-0.105	0.007	0.063	-1.223	0.086	-0.272	0.221
JCEP (2)	-0.058	0.020	0.220	-0.409	0.142	-0.336	0.683
	-0.167	0.004	-0.049	-2.764	0.060	-0.285	0.006



Meta Analysis

Supplement 20: eFigure 7. **Forest Plot: Total Symptom Improvement**

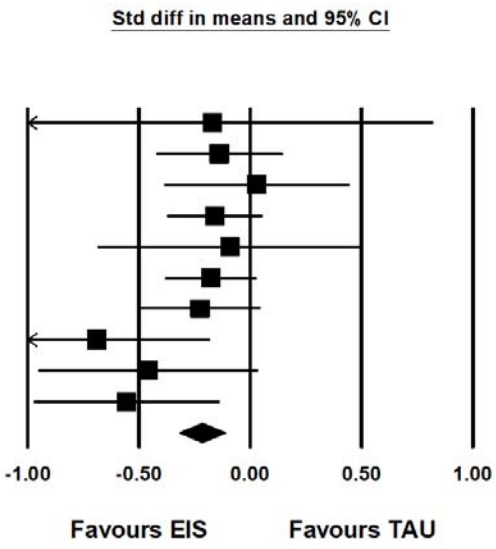
Study name	Std diff in means	Upper limit	Variance	Lower limit	Standard error	Z-Value	p-Value
Valencia 6M (10)	-0.701	-0.280	0.046	-1.122	0.215	-3.264	0.001
Valencia 12M (9)	-0.661	-0.163	0.065	-1.159	0.254	-2.601	0.009
OTP (5)	-0.534	0.050	0.089	-1.118	0.298	-1.793	0.073
STEP (8)	-0.407	0.081	0.062	-0.895	0.249	-1.635	0.102
RAISE-ETP (7)	-0.325	-0.053	0.019	-0.597	0.139	-2.343	0.019
PIANO (6)	-0.255	-0.051	0.011	-0.459	0.104	-2.455	0.014
LEO (3)	-0.106	0.309	0.045	-0.521	0.212	-0.500	0.617
JCEP (2)	-0.055	0.228	0.021	-0.338	0.144	-0.381	0.703
	-0.322	-0.170	0.006	-0.474	0.077	-4.152	0.000



Meta Analysis

Supplement 21: eFigure 8. **Forest Plot: Positive Symptom Improvement**

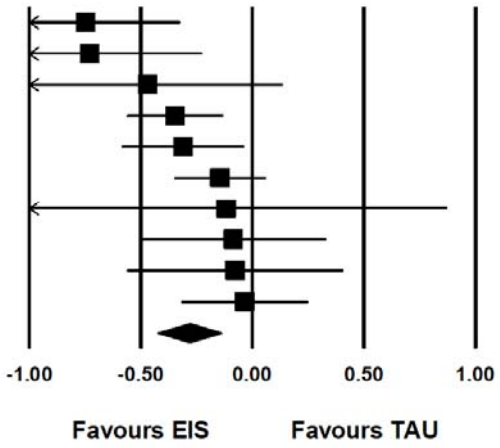
Study name	Std diff in means	Variance	Statistics for each study: Upper limit	Lower limit	Standard error	Z-Value	p-Value
COAST (1)	-0.169	0.255	0.820	-1.159	0.505	-0.335	0.738
JCEP (2)	-0.139	0.021	0.144	-0.422	0.145	-0.961	0.336
LEO (3)	0.030	0.045	0.445	-0.385	0.212	0.140	0.888
OPUS (4)	-0.159	0.012	0.054	-0.372	0.109	-1.460	0.144
OTP (5)	-0.091	0.092	0.502	-0.685	0.303	-0.301	0.763
PIANO (6)	-0.176	0.011	0.027	-0.380	0.104	-1.697	0.090
RAISE-ETP (7)	-0.225	0.019	0.046	-0.496	0.138	-1.630	0.103
STEP (8)	-0.689	0.067	-0.182	-1.196	0.259	-2.661	0.008
Valencia 12M (9)	-0.458	0.063	0.033	-0.950	0.251	-1.827	0.068
Valencia 6M (10)	-0.554	0.045	-0.138	-0.971	0.212	-2.609	0.009
.	-0.215	0.003	-0.113	-0.318	0.052	-4.111	0.000



Meta Analysis

Supplement 22: eFigure 9. **Forest Plot: Negative Symptom Improvement**

Study name	Std diff in means	Variance	Upper limit	Lower limit	Standard error	Z-Value	p-Value
Valencia 6M (10)	-0.746	0.046	-0.324	-1.169	0.216	-3.462	0.001
Valencia 12M (9)	-0.729	0.065	-0.228	-1.230	0.256	-2.851	0.004
OTP (5)	-0.469	0.095	0.136	-1.073	0.308	-1.520	0.129
OPUS (4)	-0.346	0.012	-0.131	-0.561	0.110	-3.158	0.002
RAISE-ETP (7)	-0.310	0.019	-0.038	-0.582	0.139	-2.237	0.025
PIANO (6)	-0.145	0.011	0.059	-0.349	0.104	-1.392	0.164
COAST (1)	-0.118	0.254	0.871	-1.106	0.504	-0.233	0.815
LEO (3)	-0.086	0.045	0.329	-0.501	0.212	-0.405	0.685
STEP (8)	-0.077	0.061	0.406	-0.560	0.246	-0.314	0.754
JCEP (2)	-0.034	0.021	0.249	-0.317	0.144	-0.237	0.812
	-0.280	0.005	-0.137	-0.424	0.073	-3.839	0.000



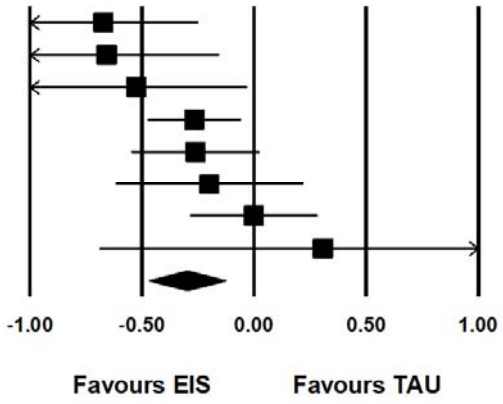
Meta Analysis

Supplement 23: eFigure 10. **Forest Plot: General Symptom Improvement**

Study name	Std diff in means	Variance	Standard error	Upper limit	Lower limit	Z-Value	p-Value
Valencia 6M (10)	-0.671	0.046	0.214	-0.251	-1.091	-3.133	0.002
Valencia 12M (9)	-0.656	0.065	0.254	-0.158	-1.154	-2.583	0.010
STEP (8)	-0.523	0.063	0.250	-0.032	-1.014	-2.089	0.037
PIANO (6)	-0.267	0.011	0.105	-0.060	-0.473	-2.533	0.011
RAISE-ETP (7)	-0.261	0.021	0.145	0.024	-0.545	-1.795	0.073
LEO (3)	-0.198	0.045	0.212	0.218	-0.614	-0.934	0.350
JCEP (2)	-0.002	0.021	0.144	0.281	-0.285	-0.012	0.990
COAST (1)	0.306	0.257	0.507	1.300	-0.687	0.605	0.545
	-0.297	0.008	0.087	-0.127	-0.468	-3.427	0.001

Statistics for each study

Std diff in means and 95% CI



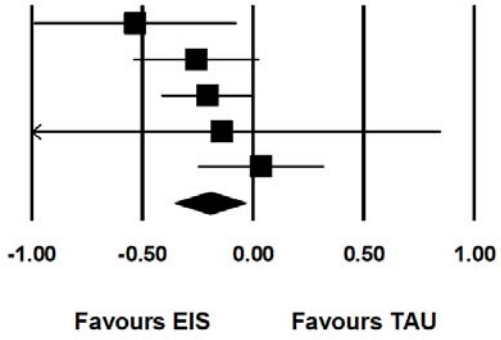
Meta Analysis

Supplement 24: eFigure 11. **Forest Plot: Depressive Symptom Improvement**

Study name	Std diff in means	Upper limit	Lower limit	Variance	Standard error	Z-Value	p-Value
LEO (3)	-0.532	-0.075	-0.988	0.054	0.233	-2.284	0.022
RAISE-ETP (7)	-0.256	0.028	-0.541	0.021	0.145	-1.766	0.077
PIANO (6)	-0.206	-0.000	-0.412	0.011	0.105	-1.961	0.050
COAST (1)	-0.141	0.848	-1.130	0.255	0.505	-0.279	0.780
JCEP (2)	0.037	0.320	-0.246	0.021	0.144	0.257	0.797
	-0.193	-0.034	-0.351	0.007	0.081	-2.386	0.017

Statistics for each study

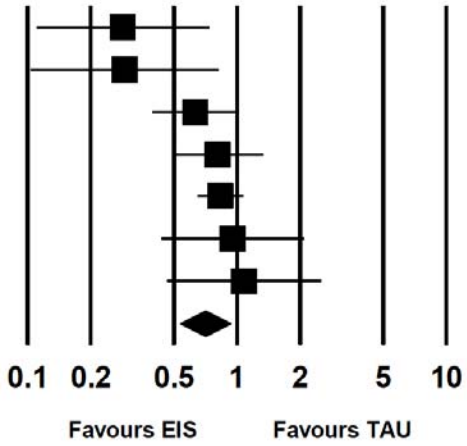
Std diff in means and 95% CI



Meta Analysis

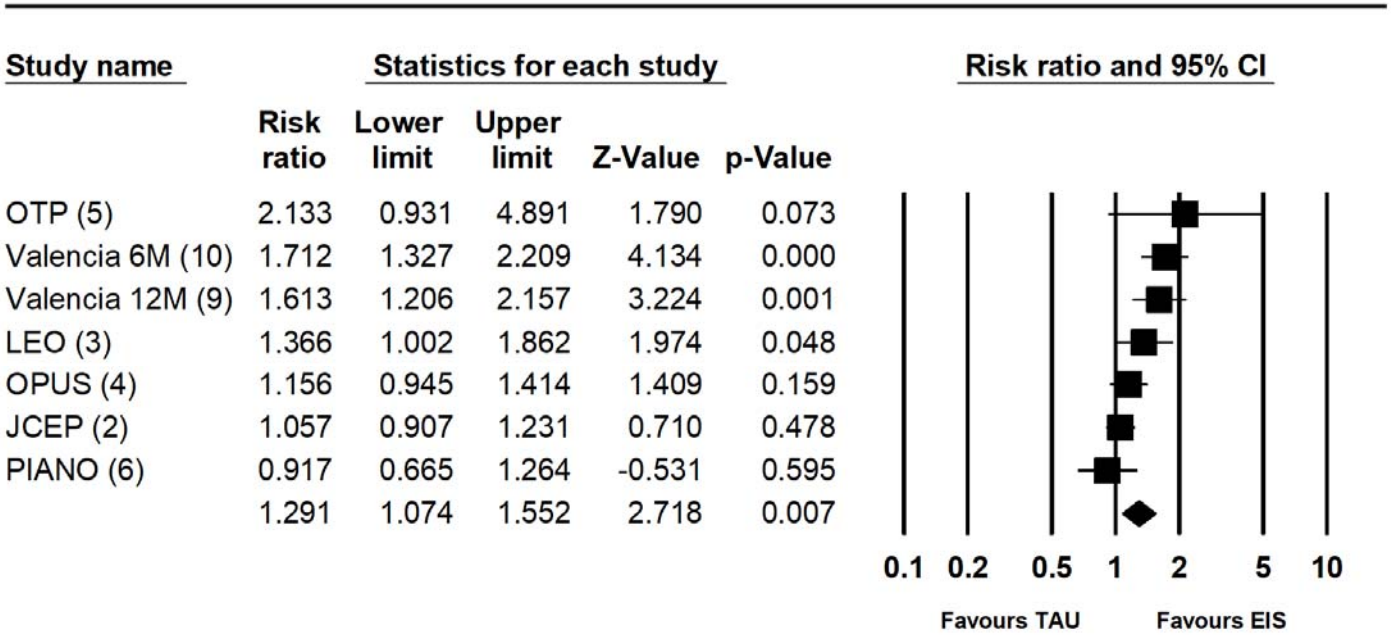
Supplement 25: eFigure 12. **Forest Plot: Relapse**

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Valencia 6M (10)	0.285	0.111	0.734	-2.599	0.009
Valencia 12M (9)	0.291	0.103	0.817	-2.343	0.019
LEO (3)	0.631	0.394	1.009	-1.921	0.055
JCEP (2)	0.808	0.490	1.333	-0.836	0.403
OPUS (4)	0.832	0.647	1.070	-1.433	0.152
OTP (5)	0.952	0.435	2.083	-0.122	0.903
PIANO (6)	1.081	0.464	2.522	0.181	0.856
	0.706	0.534	0.933	-2.452	0.014

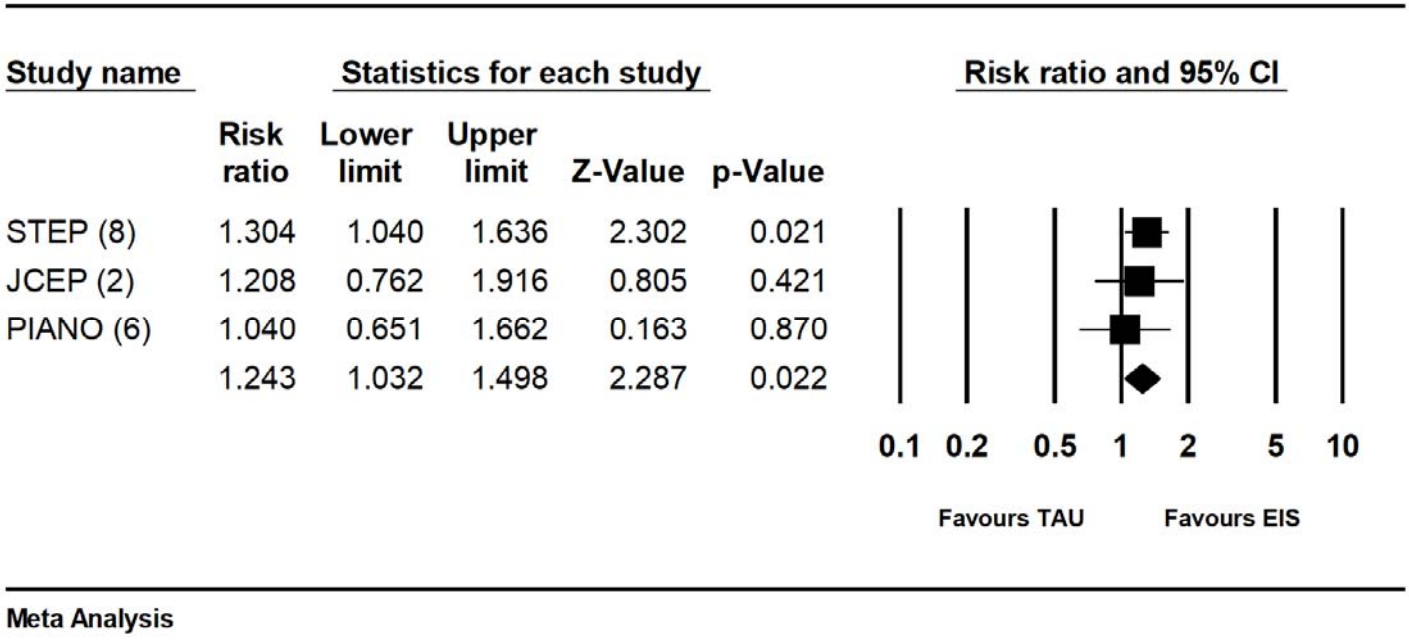


Meta Analysis

Supplement 26: eFigure 13. **Forest Plot: Remission**



Supplement 27: eFigure 14. **Forest Plot: Recovery**

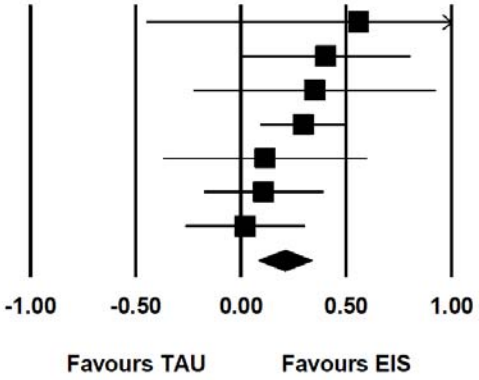


Supplement 28: eFigure 15. Forest Plot: Global Functioning

Study name	Std diff in means	Lower limit	Upper limit	Variance	Standard error	Z-Value	p-Value
COAST (1)	0.560	-0.447	1.566	0.264	0.514	1.089	0.276
LEO (3)	0.403	0.001	0.805	0.042	0.205	1.967	0.049
OTP (5)	0.351	-0.223	0.925	0.086	0.293	1.200	0.230
PIANO (6)	0.296	0.092	0.500	0.011	0.104	2.847	0.004
STEP (8)	0.115	-0.369	0.599	0.061	0.247	0.466	0.641
OPUS (4)	0.108	-0.175	0.392	0.021	0.144	0.751	0.453
JCEP (2)	0.020	-0.263	0.303	0.021	0.144	0.140	0.889
	0.210	0.085	0.336	0.004	0.064	3.280	0.001

Statistics for each study

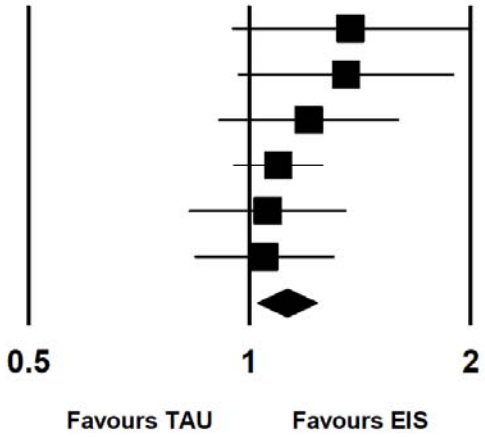
Std diff in means and 95% CI



Meta Analysis

Supplement 29: eFigure 16. **Forest Plot: Involvement in School or Work**

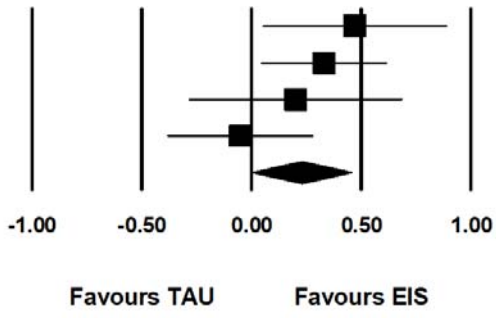
Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
LEO (3)	1.373	0.947	1.988	1.674	0.094
STEP	1.354	0.966	1.898	1.759	0.079
JCEP (2)	1.205	0.908	1.598	1.292	0.197
PIANO (6)	1.095	0.952	1.260	1.268	0.205
OPUS (4)	1.059	0.828	1.355	0.458	0.647
RAISE-ETP (7)	1.048	0.842	1.304	0.420	0.675
	1.126	1.026	1.235	2.509	0.012



Meta Analysis

Supplement 30: eFigure 17. **Forest Plot: Quality of life**

Study name	Std diff in means	Variance	Standard error	Z-Value	Upper limit	Lower limit	p-Value
LEO (3)	0.471	0.045	0.213	2.212	0.889	0.054	0.027
RAISE-ETP (7)	0.331	0.021	0.146	2.274	0.616	0.046	0.023
STEP (8)	0.202	0.061	0.247	0.816	0.686	-0.282	0.414
JCEP (2)	-0.052	0.029	0.169	-0.305	0.280	-0.383	0.760
	0.230	0.013	0.115	1.993	0.456	0.004	0.046



Meta Analysis

Supplement 31: **References (except for self-standing references in the protocol)**

1. Kuipers E, Holloway F, Rabe-Hesketh S, Tennakoon L. An RCT of early intervention in psychosis: Croydon Outreach and Assertive Support Team (COAST). *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(5):358-363. doi:10.1007/s00127-004-0754-4.
2. Craig TKJ. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*. 2004;329(7474):1067-0. doi:10.1136/bmj.38246.594873.7C.
3. Petersen L. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331(7517):602-0. doi:10.1136/bmj.38565.415000.E01.
4. Grawe RW, Falloon IRH, Widen JH, Skogvoll E. Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatr Scand*. 2006;114(5):328-336. doi:10.1111/j.1600-0447.2006.00799.x.
5. Ruggeri M, Bonetto C, Lasalvia A, et al. Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants. *Schizophr Bull*. May 2015. doi:10.1093/schbul/sbv058
6. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. *Am J Psychiatry*. October 2015:appiajp201515050632. doi:10.1176/appi.ajp.2015.15050632.
7. Srihari VH, Tek C, Kucukgoncu S, et al. First-Episode Services for Psychotic Disorders in the US Public Sector: A Pragmatic Randomized Controlled Trial. *Psychiatr Serv*. 2015. http://ps.psychiatryonline.org/doi/10.1176/appi.ps.201400236. Accessed May 14, 2015.
8. Hui CLM, Chang WC, Chan SKW, et al. Early intervention and evaluation for adult-onset psychosis: the JCEP study rationale and design. *Early Interv Psychiatry*. 2014;8(3):261-268. doi:10.1111/eip.12034.
9. Valencia M, Juarez F, Ortega H. Integrated Treatment to Achieve Functional Recovery for First-Episode Psychosis. *Schizophr Res Treat*. 2012;2012:e962371. doi:10.1155/2012/962371.
10. Valencia M, Juarez F, Delgado M, Díaz A. Early Intervention to Improve Clinical and Function-al Outcome in Patients with First Episode-Psychosis. In: *Mental Disorder*. Vol Hong Kong: iConcept Press; 2014.