

## APPENDIX 13D: CLINICAL EVIDENCE STUDY

### CHARACTERISTICS TABLES:

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#### Abbreviations

BPRS	Brief Psychiatric Rating Scale
CRT	cognitive remediation therapy
DSM (-IV)	<i>Diagnostic and Statistical Manual of Mental Disorders</i> (- 4th edition)
EPPIC	Early Psychosis Prevention and Intervention Centre, Australia
GAS	Global Assessment Scale
ITT	intention to treat
RCT	randomised controlled trial
SANS	Scale for the Assessment of Negative Symptoms
sd	standard deviation
SOFAS	Social and Occupational Functioning Assessment Scale
WAIS-III	Wechsler Adult Intelligence Scale - 3rd edition
WISC-IV	Wechsler Intelligence Scale for Children - 4th edition

## Included studies

<b>Study ID</b>	<b>EACK2009</b>
<i>Bibliographic reference</i>	Eack, S. M., Greenwald, D. P., Hogarty, S. S., <i>et al.</i> (2009) Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. <i>Psychiatric Services</i> , 60, 1468-1476.
<i>General information</i>	Funding source: National Institute of Mental Health. Published or unpublished data: Published.
<i>Method</i>	Type of study: Individual randomised trial. Type of analysis: Intention to treat (ITT). Blindness: Participants, providers and outcome assessors unblinded. Duration: Number of weeks of treatment- 104 weeks; length of follow-up - 104 weeks Raters: Independent of treatment. Design: Single-site (Pittsburg, US) randomised controlled trial (RCT). Number of people screened, excluded and reasons: Not reported. Notes about study methods: Although many participants had some college education (67%), most were not employed at baseline (74%).
<i>Participants</i>	Diagnosis: Schizophrenia (66%) or schizoaffective disorder (34%). Diagnostic tool: <i>Diagnostic and Statistical Manual of Mental Disorders</i> - 4 <sup>th</sup> edition (DSM-IV). Inclusion criteria: <ul style="list-style-type: none"> <li>• those with schizophrenia, schizoaffective or schizophreniform disorder whose illness had been stabilised on antipsychotic medication and who had experienced their first psychotic symptoms (including duration of untreated illness) within the past 8 years</li> <li>• IQ ≥80</li> <li>• not been misusing substances for at least 2 months before study enrolment</li> <li>• significant social and cognitive disability on the Cognitive Style and Social Cognition Eligibility Interview.</li> </ul> Exclusion criteria: Not reported. Total sample size: Number randomised = 58. Gender: 69% male. Age: Mean 25.9 years (range not reported). Ethnicity: 69% white. Setting: Outpatient clinic.
<i>Interventions</i>	Intervention: group 1: cognitive enhancement therapy, 60 hours of computer-assisted neurocognitive training and 45 social-cognitive group sessions, over 104 weeks, N = 31; group 2: enriched supportive therapy over 104 weeks, N = 27. Notes about the interventions: All participants received antipsychotic medications approved by the Food and Drug

	<p>Administration for the treatment of schizophrenia, schizoaffective disorder and schizophreniform disorder as indicated by a study psychiatrist. Medication changes were allowed, although every effort was made to stabilise participants on a tolerable and efficacious antipsychotic regimen before the initiation of psychosocial treatment.</p> <p>Cognitive enhancement therapy: A comprehensive, developmental approach to the remediation of social and non-social cognitive deficits in schizophrenia. Therapy typically begins with approximately 3 months of weekly 1-hour neurocognitive training in attention, after which participants begin the weekly 1.5-hour social-cognitive groups. Neurocognitive training then proceeds concurrently with social cognitive groups throughout the remaining course of treatment.</p> <p>Enriched supportive therapy: An illness management and psychoeducation approach that draws on components of the basic and intermediate phases of the demonstrably effective personal therapy. In this approach, outpatients are seen on an individual basis to learn and practice stress management techniques designed to forestall late post-discharge relapse and enhance adjustment.</p>
<i>Extractable outcomes</i>	<p>Mental state: Brief Psychiatric Rating Scale (BPRS) Depression-Anxiety and Negative Symptoms</p> <p>Psychosocial functioning: Global Assessment Scale (GAS)</p> <p>Occupation: Number of participants engaging with occupational activities (Major Role Adjustment Inventory).</p> <p>Processing speed: Composite score.</p> <p>Neurocognition: Composite score.</p> <p>Cognitive style: Composite score.</p> <p>Social cognition: Composite score.</p> <p>Social adjustment: Composite score.</p> <p>Symptoms: Composite score.</p> <p>Leaving the study early: Leaving due to any reason.</p>
<i>Quality</i>	<p>Sequence generation: Low risk.</p> <p>Allocation concealment: Low risk.</p> <p>Participants blinded: High risk.</p> <p>Providers blinded: High risk.</p> <p>Outcome assessors blinded: High risk.</p> <p>Missing outcome data: High risk.</p> <p>Selective outcome reporting: Low risk.</p> <p>Other bias: Low risk.</p>
<i>Related publications</i>	<p>Eack, S. M., Hogarty, G. E., Greenwald, D. P., <i>et al.</i> (2011) Effects of cognitive enhancement therapy on employment outcomes in early schizophrenia: results from a 2-year randomized trial. <i>Research on Social Work Practice</i>, 21, 32-42.</p>

<b>Study ID</b>	<b>KILLACKEY2008</b>
<i>Bibliographic reference</i>	Killackey, E., Jackson, H. J. & McGorry P. D. (2008) Vocational intervention in first-episode psychosis: individual placement and support v. treatment as usual. <i>The British Journal of Psychiatry</i> , 193, 114-120.
<i>General information</i>	Funding source: Medical Research Council Program and Bristol Myers Squibb. ORYGEN Research Centre is supported by the Colonial Foundation. Published or unpublished data: Published.
<i>Method</i>	Type of study: Individual randomised trial. Type of analysis: ITT. Blindness: Participants, providers and outcome assessors unblinded. Duration: Number of weeks of treatment- 26 weeks; length of follow-up - 26 weeks. Raters: Independent of treatment. Design: Single-site (Melbourne, Australia) RCT. Number of people screened, excluded and reasons: 41 individuals assessed for eligibility and all were randomised. Notes about study methods: No additional information provided by KILLACKEY2008.
<i>Participants</i>	Diagnosis: First episode psychosis (bipolar not specified). Diagnostic tool: DSM-IV. Inclusion criteria: <ul style="list-style-type: none"> <li>• aged 15-25</li> <li>• first episode psychosis</li> <li>• living in a defined catchment area</li> <li>• individuals wanted to find work (including a different job if they currently held one)</li> <li>• individuals with at least 6 months of care left at Early Psychosis Prevention and Intervention Centre (EPPIC; limited to providing 18 months of care).</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>• lack of fluency in English.</li> </ul> Total sample size: Number randomised = 41. Gender: 80.5% male. Age: Mean 21.4 years (range not reported). Ethnicity: Not reported. Setting: Specialist clinic - all were patients of EPPIC.
<i>Interventions</i>	Intervention: group 1: individual placement and support + EPPIC treatment as usual, on average the employment consultant had 29.55 (sd = 11.45) contacts with each participant, over 26 weeks, N = 20; group 2: EPPIC treatment as usual, over 26 weeks, N = 21. Notes about the interventions: Individual placement and support : A highly defined form of supported employment that has six key principles: (1) it is focused on competitive employment; (2) it is open to any person with mental illness who chooses to look for work and acceptance into the

	<p>programme is not determined by measures of work-readiness or illness variables; (3) job searching commences directly on entry into the programme; (4) the programme is integrated with the mental health treatment team; (5) potential jobs are chosen based on consumer preference; (6) the support provided in the programme is time-unlimited, continuing after employment is obtained, and is adapted to the needs of the individual. A seventh principle, also sometimes considered as part of the model of individual placement and support, is welfare benefits counselling.</p> <p>EPPIC treatment as usual: Consisted of participants continuing to receive EPPIC care. This involves individual case management and medical review, referral to external vocational agencies, as well as involvement with the group programme at EPPIC, which may involve participation in the vocationally-oriented groups within the group programme. Treatment as usual was delivered primarily by EPPIC case managers.</p>
<i>Extractable outcomes</i>	<p>Mental state: BPRS, Scale for the Assessment of Negative Symptoms (SANS), Centre for Epidemiologic Studies Depression Scale.  Quality of life: QLS.  Social Functioning: Social and Occupational Functioning Assessment Scale (SOFAS).  Employment: Number of participants, number of job interviews, weeks/hours worked, pay.  Leaving the study early: Leaving due to any reason.</p>
<i>Quality</i>	<p>Sequence generation: Low risk.  Allocation concealment: Low risk.  Participants blinded: High risk.  Providers blinded: High risk.  Outcome assessors blinded: High risk.  Missing outcome data: Low risk.  Selective outcome reporting: High risk.  Other bias: High risk.</p>
<i>Related publications</i>	None.

<b>Study ID</b>	<b>UELAND2004</b>
<i>Bibliographic reference</i>	Ueland, T. & Rund, B. R. (2004) A controlled randomized treatment study: the effects of a cognitive remediation program on adolescents with early onset psychosis. <i>Acta Psychiatrica Scandinavica</i> , 109, 70-74.
<i>General information</i>	<p>Funding source: Norwegian Research Council and the National Council for Mental Health/Health and Rehabilitation.  Published or unpublished data: Published.</p>
<i>Method</i>	<p>Type of study: Individual randomised trial.  Type of analysis: Available case.  Blindness: Participant, provider and rater unblinded.  Duration: Number of weeks of treatment - 26 weeks; length of follow-up - 52 weeks.  Raters: Independent of treatment.  Design: Single-site (Oslo, Norway) RCT.</p>

	<p>Number of people screened, excluded and reasons: Not reported.</p> <p>Notes about study methods: Patients assessed prior to discharge or after 6 months.</p>
<i>Participants</i>	<p>Diagnosis: schizophrenia (N = 16), schizoaffective disorder (N = 3), schizotypal personality disorder (N = 2), bipolar disorder (N = 3), psychotic disorder not otherwise specified (N = 1) and major depressive disorder (N = 1).</p> <p>Diagnostic tool: DSM-IV.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• aged between 12 and 18</li> <li>• a diagnosis within the schizophrenia spectrum or other psychotic disorder and no evidence of organic brain disease.</li> </ul> <p>Exclusion criteria: Not reported.</p> <p>Total sample size: Number randomised = not reported.</p> <p>Gender: 53.9% male.</p> <p>Age: Mean 15.3 years (range not reported).</p> <p>Ethnicity: Not reported.</p> <p>Setting: All participants were recruited from an inpatient unit for psychotic patients at the Sogn Centre for Child and Adolescent Psychiatry in Oslo, Norway.</p>
<i>Interventions</i>	<p>Intervention: group 1: cognitive remediation therapy (CRT) + psychoeducation, 30 hours over 26 weeks, N = 14; group 2: psychoeducation over 26 weeks, N = 12.</p> <p>Notes about the interventions: Six participants were not on medication, while 20 were receiving antipsychotic medication at baseline (ten were using atypical antipsychotics, nine were using typical antipsychotics and one was using both types).</p> <p>CRT: This group received 30 hours of individual training consisting of four modules: (1) cognitive differentiation, (2) attention, (3) memory and (4) social perception.</p> <p>Psychoeducation: Both groups received a psychoeducational treatment programme, the central elements of which were parent seminars, problem-solving sessions, milieu therapy and network groups.</p>
<i>Extractable outcomes</i>	<p>Mental state: BPRS.</p> <p>Psychosocial functioning: GAS.</p> <p>Leaving the study early: Leaving due to any reason.</p>
<i>Quality</i>	<p>Sequence generation: Low risk.</p> <p>Allocation concealment: Low risk.</p> <p>Participants blinded: High risk.</p> <p>Providers blinded: High risk.</p> <p>Outcome assessors blinded: High risk.</p> <p>Missing outcome data: Unclear risk.</p> <p>Selective outcome reporting: Low risk.</p> <p>Other bias: Low risk.</p>
<i>Related publications</i>	<p>Ueland, T. &amp; Rund, B. R. (2005) Cognitive remediation for adolescents with early onset psychosis: a 1-year follow-up study. <i>Acta</i></p>

	<i>Psychiatria Scandinavica</i> , 111, 193-201.
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<b>Study ID</b>	<b>URBEN2012</b>
<i>Bibliographic reference</i>	Urban, S., Pihet, S., Jaugey, L., <i>et al.</i> (2012) Computer-assisted cognitive remediation in adolescents with psychosis or at risk for psychosis: a 6-month follow-up. <i>Acta Neuropsychiatrica</i> , published online 4 April. DOI: 10.1111/j.1601-5215.2012.00651.x.
<i>General information</i>	Funding source: Swiss National Science Foundation. Published or unpublished data: Published and unpublished.
<i>Method</i>	Type of study: Individual randomised trial. Type of analysis: Last observation carried forward. Blindness: Participants, providers and outcome assessors unblinded. Duration: Number of weeks of treatment - 8 weeks; length of follow-up - 26 weeks. Raters: Independent of treatment. Design: Single-site (Lausanne, Switzerland) RCT. Number of people screened, excluded and reasons: Not reported. Notes about study methods: No additional information provided by URBEN2012.
<i>Participants</i>	Diagnosis: Psychotic disorder (65%), at high risk of developing psychosis (35%). Diagnostic tool: DSM-IV. Inclusion criteria: <ul style="list-style-type: none"> <li>• diagnosis of psychotic disorder according to DSM-IV using the French version of Diagnostic Interview for Genetic Studies</li> <li>• diagnosis of high risk of psychosis using the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms</li> <li>• a score below the 10<sup>th</sup> percentile in at least one of five domains of the Repeatable Battery for the Assessment of Neuropsychological Status.</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>• 'mental retardation' (IQ &lt; 70)</li> <li>• known neurological disease or developmental disability</li> <li>• severe visual or motor disorder that is incompatible with computer use</li> <li>• transient exclusion criteria: an acute clinical state that could disrupt the computer-assisted cognitive remediation training or a planned absence for more than 2 weeks during period of intervention.</li> </ul> Total sample size: Number randomised = 32. Gender: 64% male. Age: Mean 15.61 years (range 13 to 17). Ethnicity: Not reported. Setting: Outpatient clinic.
<i>Interventions</i>	Intervention: group 1: Computer-assisted cognitive remediation program, two 45-minute individual sessions per week over

	<p>8 weeks (16 individual sessions), N = 18; group 2: computer games, two 45-minute individual sessions per week over 8 weeks (16 individual sessions), N = 14.</p> <p>Notes about the interventions:</p> <p>Computer-assisted cognitive remediation: The program was based on the Captain's Log software and allows training in attention, concentration, memory, visuospatial, visuomotor and conceptualisation with increasing difficulty.</p> <p>Computer games: A set of action computer games (N = 13), requiring attention and visuomotor skills were used as control.</p>
<i>Extractable outcomes</i>	<p>Mental state: Positive and Negative Syndrome Scale, Scale for the Assessment of Positive Symptoms, SANS</p> <p>Global state: Clinical Global Impression Severity scale.</p> <p>Social functioning: SOFAS.</p> <p>Occupation: Number of participants engaging with occupational activities.</p> <p>Processing speed: The symbol coding test (Wechsler Adult Intelligence Scale – 3<sup>rd</sup> edition [WAIS-III]: &gt;16 years / Wechsler Intelligence Scale for Children – 4th edition [WISC-IV]: &lt;16 years old).</p> <p>Working memory: Letter-number sequencing (WAIS-III: &gt;16 years old/WISC-IV: &lt;16 years old).</p> <p>Long-term memory: The Hopkins Verbal Learning Test-Revised. The Brief Visuospatial Memory Test-Revised was used to assess visuospatial episodic memory.</p> <p>Executive functions: The Color Stroop task.</p> <p>Reasoning and planning abilities: The block design test (WAIS-III/WISC-IV).</p> <p>Neurocognition: Composite score.</p> <p>Cognitive style: Assessed cognitive functions were processing speed, memory abilities and executive function.</p> <p>Leaving the study early: Leaving the study early for any reason.</p>
<i>Quality</i>	<p>Sequence generation: Unclear risk.</p> <p>Allocation concealment: Unclear risk.</p> <p>Participants blinded: High risk.</p> <p>Providers blinded: High risk.</p> <p>Outcome assessors blinded: Low risk.</p> <p>Missing outcome data: High risk.</p> <p>Selective outcome reporting: Low risk.</p> <p>Other bias: High risk.</p>
<i>Related publications</i>	<p>Holzer, L., Passini, M. C., Pellanda, V. <i>et al.</i> A randomised controlled trial of the effectiveness of a computer-assisted cognitive remediation (CACR) program in adolescents with psychosis or at high risk of psychosis. <i>Behaviour Research and Therapy</i> (submitted).</p>



<b>Study ID</b>	<b>WYKES2007</b>
<i>Bibliographic reference</i>	Wykes, T., Newton, E., Landau, S., <i>et al.</i> (2007) Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial. <i>Schizophrenia Research</i> , 94, 221-230.
<i>General information</i>	Funding source: Mental Health Foundation. Published or unpublished data: Published.
<i>Method</i>	Type of study: Individual randomised trial. Type of analysis: ITT. Blindness: Participants, providers and raters not blind. Duration: Number of weeks of treatment – 14 weeks; length of follow-up – 26 weeks. Raters: Independent of treatment. Design: Single-site (London, UK) RCT. Number of people screened, excluded and reasons: 66 people referred, 40 met criteria and consented (16 did not meet clinical criteria, six did not consent, four did not meet cognitive criteria); 40 people randomised. Notes about study methods: Symptom and quality of life assessments were assessed by an independent rater who was blind to group allocation. Self-report assessments (cognition and self-esteem) and informant ratings (social behaviour) were collected by a research assistant who was not blind to group allocation.
<i>Participants</i>	Diagnosis: Schizophrenia. Diagnostic tool: DSM-IV. Inclusion criteria: <ul style="list-style-type: none"> <li>• diagnosis of schizophrenia with an onset prior to the age of 19 and a duration of illness of 3 years or less</li> <li>• difficulties in cognitive flexibility (as demonstrated by a score below the 16th percentile on the Wisconsin Card Sort Test and/or memory (as demonstrated by a score falling within the 'poor' performance range or below on the screening test of the Rivermead Behavioural Memory Test)</li> <li>• difficulties in social functioning (identified as having at least one problem on the Social Behaviour Schedule</li> <li>• on a stable dose and type of medication, for at least 1 month prior to inclusion.</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>• a history of organic brain disorder (for example, epilepsy)</li> <li>• a diagnosis of current substance abuse as defined by the DSM-IV.</li> </ul> Total sample size: Number randomised = 40 Gender: 65% male. Age: Mean 18.2 (range 14 to 22) years. Ethnicity: Not reported. Setting: Inpatient.
<i>Interventions</i>	Intervention – group 1: CRT, 40 hourly sessions over 14 weeks, N = 21; group 2: treatment as usual, over 14 weeks, N = 19.

	Notes about the interventions: CRT: Forty 1-hour sessions, at an average rate of three per week. In each session, a variety of tasks was presented to practice the component processes in remembering, complex planning and problem solving. The tasks were graded in difficulty with easier ones being presented early in the programme. Treatment as usual: Details not reported.
<i>Extractable outcomes</i>	Leaving the study early: Leaving due to any reason.
<i>Quality</i>	Sequence generation: Unclear risk. Allocation concealment: Low risk. Participants blinded: High risk. Providers blinded: High risk. Outcome assessors blinded: High risk. Missing outcome data: High risk. Selective outcome reporting: High risk. Other bias: Low risk.
<i>Related publications</i>	None.

## Excluded studies

A generic search was conducted in order to address review questions across each section of the guideline. Studies assessing cognitive, educational and occupational outcomes were identified from a list of included RCTs of pharmacological, psychological, psychosocial or dietary interventions (see Appendices 13b and 13c) and therefore no list of excluded studies was generated for Appendix 13d.