# Appendix Table E-22. Data abstraction of randomized controlled trials of early interventions for patients with first-episode psychosis

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| Early  Treatment Program  (ETP)-RAISE  Kane 2015, 2016 | U.S. | 1) Ages 15-40  2) ability to participate in research assessments in English  3) ability to full consent (or assent if under  18)  4) presence of definite psychotic symptoms and evidence of one of following diagnoses: schizophrenia, schizoaffective disorder, schizophreniform, psychotic disorder NOS, or brief psychotic disorder (DSM-IV)  5) up to 6 months of cumulative exposure to antipsychotic medications.  First-episode schizophrenia spectrum (89% for NAVIGATE, 90% for standard care) Schizophrenia-only: NAVIGATE (51%), standard care (56%) | By participant:  NAVIGATE (n=223), Community Care (n=181)  Cluster randomization by site:  NAVIGATE (n=17), Community Care (n=17) | NAVIGATE model includes four core interventions delivered by a multidisciplinary team: personalized medication management via a secure web-based decision support system, family psychoeducation, individual resiliency therapy, and supported employment and education. |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| Early  Treatment Program  (ETP)-RAISE  Kane 2015, 2016 | Called "Community Care;"  Standard care for psychosis treatment | 2 years | Demographics (intervention, control)  Mean age: 23.18, 23.08  Gender/males: 78%, 66% (significantly more males in NAVIGATE) Race/ethnicity:  White=62%, 44%  African American=28%, 49% Other=10%, 7% Hispanic=25%, 10% | (intervention, control)  Weeks of duration of untreated psychosis:  178.91, 211.43  Heinrich-Carpenter QLS total: 18.44, 18.99  PANSS total: 14.95, 14.87 (significantly worse for NAVIGATE)  Calgary Depression Scale: 4.27, 4.30  CGI: 0.80, 0.83  Duration of time on antipsychotics (days):  42.88, 48.98  Patient's education:  College or higher: 32%, 30% Completed high school: 34%, 32% Some high school: 30%, 32%  Lifetime alcohol use (did not meet criteria):  60%, 68%  Lifetime cannabis use (did not meet criteria):  61%, 68% | 404 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Early  Treatment Program  (ETP)-RAISE  Kane 2015, 2016 | **Treatment retention:** NAVIGATE participants remained in treatment significantly longer (median=23 months) than community care participants (median=17 months) (p<0.004).  **Quality of life (Heinrich’s QLS):** NAVIGATE participants experienced significantly greater improvement in quality of life (change score=15.793) than those in community care (change score=9.891) during the 2-year assessment period (p=0.0145).  **Employment/education:** A higher proportion of NAVIGATE participants were either working or going to school at any time during each month over the 2-year period compared to community care participants (group by time interaction, p=0.044). These data do not reflect change over time within participant, only the end point each month.  **Psychotic symptoms (PANSS):** NAVIGATE participants experienced greater improvement on PANSS total scores (change score=-14.313) compared to standard care (change score=-9.989) at 2 years (p=0.0161).  **Depressive symptoms (Calgary Depression Scale for Schizophrenia):** NAVIGATE participants experienced significantly greater improvement in depressive symptoms (change score=-1.981) compared to standard care (change score=-1.196) (p=0.0318). | None reported. | NIMH | Poor |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| Guo 2007, 2010 | 10 clinical  sites in China | 1) Ages 16-50  2) DSM-IV criteria for schizophrenia, or schizophreniform disorder for not more than  5 years  3) being confirmed to be clinically  stable by the investigator (the total score ≤60 on the PANSS or a decrease of 50% from acute period in the total score on PANSS  4) taking maintenance therapy with any one of the following seven oral antipsychotics: chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, quetiapine, and aripiprazole. First episode schizophrenia  84.6%, schizophreniform 15.4% | Combined Treatment  (n=604), Medication  Treatment (n=635) | Antipsychotic medication plus group psychoeducation, family intervention, skills training, and CBT (Once a month x 12 months, 48 sessions total). |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| Guo 2007, 2010 | Antipsychotic medication  only | 12 month  intervention only | Demographics (intervention, control)  Age, mean years: 26.1, 26.4  Gender, % Male: 54.3%, 55.7% Race/ethnicity: NR | (Intervention, control)  Age at onset: 23.8, 24.2  Duration of schizophrenia: 24.6 months, 23.3 months  PANSS total score: 44.7, 45.6  CGI severity score: 2.5, 2.6 | 1268 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Guo 2007, 2010 | **Discontinued treatment**: Rates of treatment discontinuation or change due to any cause were 32.8% (198) for combined treatment group vs. 46.8% (297) for medication treatment (HR 0.62; 95% CI 0.52-0.74; p<0.001)  **Relapse:** Risk of relapse was lower among participants assigned to combined treatment (14.6%; 88) vs. medication treatment (22.5%; 143) (HR 0.57; 95% CI 0.44-  0.74; p<0.001)  **Psychotic symptoms (PANSS):** No significant difference over time between combined treatment (34.7) and medication treatment (36.4; F=0.41, p=0.81)  **Insight (Insight and Treatment Attitudes Questionnaire [ITAQ]):** Change in total ITAQ (poor insight) scores was significantly greater over time for combined treatment group (19.5) than in medication treatment (15.9; F=25.94; p<0.001).  **Social functioning (Global Assessment Scale):** Combined treatment (82.9) showed significant improvement over time vs. medication treatment (80.8; F=4.33; p=0.002)  **Activities of Daily Living (ADL scale) scores:** Combined treatment (15.4) showed significant improvement over time vs. medication treatment (16.4; F=12.70; p<0.001)  **Employment and education:** A significantly higher proportion of patients receiving combined treatment obtained employment or accessed education (30.1%) compared to those receiving medication treatment (22.2%; X 2=10.09; p=0.001). | Extrapyramidal symptoms: No significant differences between combined treatment (135) and medication treatment (142; X2=0.20, p=0.66).  Weight gain >7% from baseline to last observation: No significant differences between combined treatment (149) and medication treatment (132; X2=1.39, p=0.24). | Grants from National  Key Technologies R&D Program, National Natural Science Foundation of China, and the National Basic  Research Program of  China | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) trial  Craig 2004 | England | 16-40 years living in the London borough of Lambeth and presenting to mental health services for the first time with nonaffective psychosis (schizophrenia, schizotypal, and delusional disorders). Also considered people who had presented once but had subsequently disengaged without treatment from routine community services.  Schizophrenia:  Specialized care = 51 (72%) Standard care = 49 (67%) | Early intervention  specialized care (n=71); Standard care (n=73) | Community team of 10 staff (team leader, 0.5 consultant psychiatrist, trainee psychiatrist, 0.5 clinical psychologist, OT, four psychiatric nurses, two healthcare assistants). Established on the principles of assertive outreach, providing an extended hours service by including weekends and public holidays. Evidence-based interventions adapted to the needs of people with early psychosis included low- dose atypical antipsychotic regimens, CBT based on manualized protocols, and family counseling and vocational strategies based on established protocols. |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) trial  Craig 2004 | Standard care delivered by the community mental health teams. Teams received no additional training in the management of early psychosis, although they were encouraged to follow available guidelines | 18 months | (intervention, control)  Mean age: 26 (6.0), 26.6 (6.4) Gender: Male, 39 (55%), 54 (74%) Race/ethnicity:  White 27 (38%) 18 (25%) Black British 10 (14%) 6 (8%)  Black Caribbean 9 (13%) 13 (18%) Black African 16 (23%) 25 (34%) Mixed 6 (8%) 6 (8%)  Other 3 (4%) 5 (6%) | (intervention, control)  First episode: 61 (86%) 52 (71%) | 144 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) trial  Craig 2004 | **Relapse:** Participants in the specialized care group were less likely to relapse (30%,  18 out of 61) than those in standard care (48%, 29 out of 61) (odds ratio 0.46, 95% CI  0.22 to 0.97; p=0.042). When rates were adjusted for baseline differences in sex, previous psychotic episode, and ethnicity, the difference in relapse was no longer significant (odds ratio 0.55, 95% CI 0.24 to 1.26, p=0.157).  **Retention in treatment/dropout:** At 18 months, 53 (86%) patients in the specialized group and 44 (68%) in standard care were in regular contact with the clinical team (lost to care: odds ratio 0.35, 95% CI 0.15 to 0.81). When rates were adjusted for baseline differences in sex, previous psychotic episode, and ethnicity, drop-out rates remained significant (0.28, 95% CI 0.12 to 0.73). | None reported. | Directorate of Health  and Social Care for London R&D Organisation and Management Programme | Good |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) Trial  Garety 2006 | England | 16–40 years with an address in Lambeth for the first time with a nonaffective psychosis. Patients who met these demographic and diagnostic criteria who had presented once previously but had immediately disengaged and were not known to any of the existing mental health services were also deemed eligible.  Majority met ICD–10 diagnostic criteria for schizophrenia (69%) | LEO/specialized care  (n=55), standard care group (n=44) | A multidisciplinary team providing assertive outreach, a single point of access, and extended service hours. The interventions provided were specially adapted for a group with early psychosis and followed protocols and manuals from the Early Psychosis Prevention and Intervention Centre and, for CBT, pilot work conducted locally. A mix of medication management, CBT, vocational input and family interventions was provided according to individual need. |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) Trial  Garety 2006 | Standard care by community mental health teams. | 18 months | Average age: 26 years  Gender: Male (65%)  More than 50% were from a minority ethnic, predominantly  of African or Caribbean parentage. | (intervention, control)  First episode: 61 (86%) 52 (71%) PANSS Total: 67.4, 73.3  GAF: 46.5, 42.2  Calgary Depression Scale: 4.1, 3.3 | 99 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) Trial  Garety 2006 | **Psychotic symptoms (PANSS scores):** No significant differences between specialized care (51.2) and standard care (58.9) at 18 months (F=5.74, 95% CI -0.30 to 11.79, p=0.06). This result attenuates when adjusting for baseline differences in ethnicity, gender, and episode (F=5.26, 95% CI 71.14 to 11.65; p=0.11).  **Social functioning (GAF scores):** Significantly improved for specialized care (64.1) vs. standard care (55.3) at 18 months (F=-8.72, 95% CI 15.46 to -1.98; p=0.01), even when adjusting for baseline differences (F=-8.77, 95% CI -15.89 to -1.65; p=0.02).  **Calgary Depression Scale scores:** No significant differences between specialized care (2.7) and standard care (2.7) at 18 months (F=0.93, 95% CI -0.47 to 2.33, p=0.19), a trend that continued when adjusting for baseline differences (F=0.98, 95% CI -0.51 to 2.47, p=0.19).  . | Reported on deaths, prison, self-harm, violence to others and homelessness, but no statistical tests conducted. | Directorate of Health  and Social Care for London R&D Organisation and Management Programme | Good |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Lambeth Early Onset  (LEO) Trial  Garety 2006  Continued | **Insight (Scale for the Assessment of Insight scores):** No significant differences between specialized care (16.6) and standard care (12.7) at 18 months (F=-2.94,  95% CI 76.20 to 0.31; p=0.076), including when adjusting for baseline differences (F=-  2.45, 95% CI -5.94 to 1.05; p=0.167).  **Quality of life (Manchester Short Assessment of Quality of Life [MANSA]**  **scores):** Significantly improved for specialized care (59.2) vs. standard care (53.3) at  18 months (F=-5.96, 95% CI 11.19 to -0.74), p=0.026, even when adjusting for baseline differences (F=-7.08, 95% CI -12.47 to -1.69, p=0.011).  **Vocational/educational outcomes:** No significant differences between specialized care (33%; 21 out of 64) and standard care (21%; 13 out of 61) on vocational/educational outcomes at 18 months (x 2=2.086 [df=1], p=0.170); however, specialized care spent significantly more time in vocational and educational activity (6.9 months, SD=6.6; n=67) than standard care (4.2 months, SD=5.3; n=65); t=2.689, p=0.008 at 18 months.  **Housing outcomes:** No significant differences between specialized care (70%; 46 out of 66) and standard care (58%; 36 out of 62) on housing outcomes at 18 months (x2=1.879 [df=1], p=0.170) at 18 months.  **Relationships outcomes:** 55% (34 out of 62) of participants in specialized care engaged in social relationships vs. 25% (14 out of 57) at 18 months (x2=11.31, [df=1], p<0.001). | see above | see above | see above |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| Secondary analysis  of subset of participants from the Lambeth Early Onset (LEO) Trial  Tempier 2012 | England | Residents of the London borough  of Lambeth, ages 16-40, presented to mental health services with  a first episode of nonaffective psychosis between January 2000 and October  2001. | Specialized care  (n=57), standard care  (n=50) | Specialized early intervention following the ACT model, including an interdisciplinary team, low patient-to-staff ratios and high availability of individualized care.  Team adhered to Maudsley Prescribing Guidelines, and had access to good practice guidelines for the wider psychosocial management of first-episode psychosis, psychological advice, and CBT. |
| OPUS  Bertelsen, 2009 | Multicenter  Denmark | Age 18-45 years, first use of mental health  services, diagnosis within the schizophrenia spectrum, and no prior use of antipsychotics for more than 12 weeks | Intensive early  intervention program  (n=275) Standard care (n=272) | Intensive intervention, including assertive community  treatment, family treamtent, social skills training, and antipsychotics |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| Secondary analysis  of subset of participants from the Lambeth Early Onset (LEO) Trial  Tempier 2012 | Standard care provided by a generic community mental health team. Team adhered to Maudsley Prescribing Guidelines, and had access to good practice guidelines for the wider psychosocial management of first-episode psychosis, psychological advice, and CBT. | 6- and 18-month  followup | Demographics (intervention, control)  Mean age: 25.7, 26.0  Gender/males: 53%, 78% (significantly more males in standard care) Race/ethnicity:  White=42%, 24% (difference not statistically significant)  Black=42%, 58% Other=16%, 18% | None reported. | 107 |
| OPUS  Bertelsen, 2009 | Standard treatment at a  community mental health center, including antipsychotics | Intervention: 2  years  Follow-up: 5 years | Demographics (intervention, control)  Mean age: 26.6 years, 26.6 years Female sex: 42%, 40% Race/ethnicity: NR | (Intervention, control)  Inpatient at randomization: 43%, 47% Median duration of untreated psychosis: 46 weeks, 53 weeks  Schizophrenia diagnosis: 67%, 65% Substance abuse: 27%, 27% | 547 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| Secondary analysis  of subset of participants from the Lambeth Early Onset (LEO) Trial  Tempier 2012 | **Psychotic symptoms (PANSS Total score):** Participants in specialized care experienced significant improvement in symptoms (51.60±15.41) compared to those in standard care (59.70±14.12), t=2.51, df=85, p=0.01) at 18 months.  **Functioning (GAF):** Participants in specialized care experienced significant improvement in functioning (64.20±15.23) compared to those in standard care (55.89±14.04), t=2.59, df=85, p=0.01) at 18 months.  **Social networks:** Significantly larger social networks for those in specialized care  (2.40+1.2) vs. standard care (1.71+1.06) t=2.77, df=84, p=0.01) at 18 months. | None reported. | Directorate of Health  and Social Care for London R&D Organisation and Management Programme | Fair |
| OPUS  Bertelsen, 2009 | **End of intervention (2 years)**  GAF, symptoms: 51.2 vs. 48.7; mean difference 2.45 (95% CI -0.32 to 5.22) GAF, function: 55.2 vs. 51.1; mean difference 3.12 (95% CI 0.37 to 5.88)  **End of follow-up (5 years)**  GAF, symptoms: 53.5 vs. 53.8; mean difference -0.16 (95% CI -3.97 to 3.37) GAF, function: 55.4 vs. 54.2; mean difference 1.34 (95% CI -2.65 to 5.34)  Not living independently: 4% vs. 10%; OR 2.3 (95% CI 1.1 to 4.8) p=0.02  Unemployed: 57% vs. 54%; OR 1.1 (95% CI 0.8 to 1.6) p=0.57  Suicide attempts: 9% vs. 9%; OR 0.9 (95% CI 0.4 to 2.1) p=0.86 | NR | Danish Ministry of  Health; Danish Ministry of Social Affairs; University of Copenhagen; Copenhagen Hospital Cooperation; Danish Medical Research Council; Slagtermester Worners Foundation; and the Stanley  Wada Research  Foundation | Good |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per Group** | **Description of Intervention** |
| --- | --- | --- | --- | --- |
| OPUS  Secher 2015 (Note: Referred to  description of OPUS  trial in Peterson,  2005; did not include Peterson due to its inclusion in SR) | Denmark | 18–45 years of age, recent first diagnosis within the schizophrenic spectrum (F2X.X in ICD-10), and at most 12 consecutive weeks of antipsychotic medication. In the 10-year followup study reported here, interviewed  68% of the participants who were alive and lived in Denmark.  First episode psychosis, including: Schizophrenia (67% OPUS, 65% usual care), Schizotypal (15% OPUS, 14% usual care), Brief Psychosis (7% OPUS, 10% usual care) | OPUS (n=181), usual  care (n=166) Included in ITT: OPUS (n=275), usual care (n=272) | Enhanced ACT, multi-family group psychoeducation, and social skills training. Also offered CBT and supportive therapy if needed. Staff-to-client ratio = 1:10. Antipsychotic medication based on same principles for both groups. |

| **Author, Year** | **Description of Comparator** | **Duration** | **Age Gender Race/Ethnicity** | **Other Population Characteristics** | **Total N** |
| --- | --- | --- | --- | --- | --- |
| OPUS  Secher 2015 (Note: Referred to  description of OPUS  trial in Peterson,  2005; did not include Peterson due to its inclusion in SR) | Usual care in community mental health, staff-to-client ratio = 1:30. Antipsychotic medication based on same principles for both groups. | Intervention  length: 2 years Followup at 10 years | Demographics: (intervention, control)  Mean age: 26.6 for both conditions  Males: 58% for OPUS, 60% for usual care  Race/ethnicity: Not reported | (intervention, control)  Median duration of untreated psychosis  (duration of untreated psychosis; weeks): 46,  53  Psychopathology scores (SAPS/SANS) summarized into three dimensions: Psychotic dimension: 2.8, 2.6  Negative dimension: 2.2 for both  Disorganized dimension: 1.0 for both  Substance Abuse Diagnosis:  27% for both  Education:  None: 60%, 59%  Currently being educated: 14%, 12% Short education/skilled: 20%, 20% Longer education: 6%, 9% | 347 |

| **Author, Year** | **Benefits Outcomes** | **Harms Outcomes** | **Funding** | **Quality**  **Rating** |
| --- | --- | --- | --- | --- |
| OPUS  Secher 2015 (Note: Referred to  description of OPUS  trial in Peterson,  2005; did not include Peterson due to its inclusion in SR) | Functioning (GAF): At 10-year followup there were no significant differences in GAF functioning scores between OPUS (54.33) and usual care participants (54.65), (estimated mean difference=-0.76, 95% CI -4.01 to 2.49, p=0.65).  Supported Housing: At 10-year followup, mean number of days in supported housing was not significantly different for OPUS (14.1) vs. usual care (20.8) (B=-6.63, 95% CI -  19.86 to 6.61, p=0.30). The mean number of days in supported (vs. institutional) housing from year 1 to year 10 was statistically significant in favor of OPUS (p<0.01); however, the difference at years 4 and 5 account for much of this finding.  Employment/Education: At 10-year followup, there were no significant differences between OPUS (35.3%; 90) and usual care (35.8%; 87) participants regarding proportion working or studying (OR 0.99, 95% CI 0.67 to 1.45, p=0.97). | Deaths: After 10 years, 14  OPUS participants (5.1%) were deceased vs. 15 usual care participants (5.5%), p=0.83. Suicidal ideation: The proportion of participants who, at 10-year followup, had experienced suicidal ideation within the preceding two years was similar to OPUS (39.4%) and in usual care (379%), p=0.77. | Danish Council for  Independent Research; Trygfonden; The Mental Health Services of the Capital Region of Denmark; the Danish  Ministry of Health; the Danish Ministry of Social Affairs; the Psychiatry and Social Service Dept in Central Denmark Region | Good |

**Please see Appendix B. Included Studies for full study references**

ACT=assertive community treatment, CBT=cognitive behavioral therapy, CGI=clinical global impression, CI=confidence interval, df=degrees of freedom, ETP=early treatment program, F=fixation index, GAF=global assessment of functioning, HR=hazard ratio, ITT=intention to treat, LEO=Lambeth Early Onset, NIMH=National Institute of Mental Health, NOS=not otherwise specified, OPUS=Specialized Early Intervention Trail, OR=odds ratio, OT=occupational therapy, PANSS=positive and negative syndrome scale, QLS=quality of life scale, R&D=research and development, SAPS=Scale for the Assessment of Positive Symptoms, SANS=Scale for Assessment of Negative Symptoms, SD=standard deviation, SR=systematic review, U.S.=United States