2023

OPUS YOUNG

EFFICACY OF EARLY INTERVENTION SERVICE VERSUS TREATMENT AS USUAL FOR ADOLESCENTS AGED 12-17 YEARS WITH A FIRST-EPISODE PSYCHOSIS. AN INVESTIGATOR-INITIATED, RANDOMIZED CLINICAL TRIAL.

PROTOCOL VERSION 6.1 – JULY 2023
The Ethics Committee of Capital Region: H-20064085 (20-04-2021)
Danish Data Protection Agency: P-2020-1081 (20-11-2020)

07-07-2023

Abbreviations

ADM	Administration modus
AMHS	Adult Mental Health Services
BACS	Brief Assessment of Cognition in Schizophrenia
BRIEF	Behavior Rating Inventory of Executive Function
CAMHC	Child and Adolescent Mental Health Center
CBT	Cognitive Behavioral Therapy
CBCM	Cognitive Behavioral Case Management
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CHU-9D	The Child Health Utility
CRF	Case Report Form
CVI	Central Visitation Unit
ECG	Electrocardiogram
EIMT	Emotional Intensity Morphing Task
EIS	Early Intervention Services
EOP	Early Onset of Psychosis
ESQ	Experience of Service Questionnaire
EQ-5D	European Quality of life - 5 Dimensions
FAD	McMaster Family Assessment Device
FEP	First Episode Psychosis
GCP	Good Clinical Practice Guideline
GSE	General Self-Efficacy Scale
HAM-D	Hamilton Depression Scale
ICC	Interclass Correlation Coefficient
ICD 10	International Classification of Diseases - 10
IRAOS	Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses
KIDSCREEN-10	Health-related Quality of Life Screening Instrument for Children and Adolescents (10 items)
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged children, Present and Lifetime Version
MET	Motivational Enhancement Therapy
MFG	Multifamily group
MIREDIF	Minimal Relevant Difference
NEQ	Negative Effects of psychological treatment Questionnaire
PSS	Parental Stress Scale

PSP	Personal and Social Performance Scale
REDCap	Research Electronic Data Capture
RCT	Randomized Clinical Trial
SAPS	Scale for the Assessment of Positive Symptoms
SANS	Scale for the Assessment of Negative Symptoms
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard Deviation
SCIT	Social Cognition and Interaction Training
SST	Social Skills Training
TAU	Treatment As Usual
TEM	Trivsels- og Effekt Monitorerings-skemaet
ToM	Theory of Mind
WAI	Working Alliance Inventory Scale
WAIS-IV	Wechsler Adult Intelligence Scale, IV
WISC-V	Wechsler Intelligences Scale for Children, V
YMRS	Young Mania Rating Scale

Summary

The overarching purpose of the OPUS YOUNG trial is to improve the treatment and outcome of first-episode psychosis (FEP) in children and adolescents. We will address this ambition by testing the hypothesis, that Early Intervention Services (EIS) is superior compared to standard care in the treatment of children and adolescents below age 18 years with first-episode psychosis. The hypothesis is based on extrapolation of research showing that EIS is superior to standard care in the treatment of adults with first-episode psychosis with regards to symptom reduction, function improvement, adherence to treatment, lower hospitalization risk, improved recovery, and higher cost-effectiveness. However, no trials have investigated EIS in samples of patients below age 18 years. We will compare the efficacy and cost-effectiveness of EIS to treatment as usual (TAU) in adolescents aged 12-17 years (both inclusive) with first-episode psychosis. We will build on a Danish evidence-based intervention developed for young adults (OPUS) and adjust the concept to meet the specific needs of children and adolescents with early onset psychosis (OPUS YOUNG). The OPUS treatment is a coordinated and integrated manualized multimodal treatment building on three core elements: modified assertive community treatment with a low patient-case manager ratio; psychoeducational family intervention; and social skills training (SST). In OPUS YOUNG we will adjust the OPUS program to fit our younger age group by: 1) intensifying the support for caretakers and relatives including siblings, 2) instead of SST we are introducing social cognition and interaction treatment (SCIT), 3) providing individual cognitive behavioural case management (CBCM) to all participants and cognitive behavioural therapy (CBT) when needed, 4) addressing the specific challenges of psychopharmacologic treatment in adolescents by providing a treatment algorithm, 5) providing intensive supported transition of care (when patients approach transition to adult mental health services), 6) providing individualized school support, and 7) providing integrated prevention and treatment of substance misuse. Based on sample size estimation, we will include a minimum of 284 participants (maximum 304) and randomize them 1:1 to a two-year intervention of OPUS YOUNG versus TAU. We will conduct blinded assessment of treatment effects after 12 months and at treatment endpoint at 24 months. A further follow-up assessment will be performed to evaluate the sustainability of the intervention effects at six months after transition from OPUS YOUNG to TAU. Our primary outcome at treatment endpoint will be social function measured with Personal and Social Performance Scale (PSP). Secondary key outcomes measures are positive and negative symptoms, client satisfaction, and health related quality of life. Further outcomes are the broader psychopathology, cognitive functioning, social cognition, self-efficacy,

experience of service, treatment alliance and adherence, the use of pharmacotherapy, school adherence, family burden, siblings' perceived stress, substance misuse, adverse treatment effects, and health economic measures.

Purpose

The overarching purpose of this study is to improve the treatment outcomes in first-episode psychosis in children and adolescents, and to reduce illness socio-economic burden.

Background

Early onset of psychosis in childhood and adolescence (i.e., before age 18 years) is associated with the same clinical, cognitive, aetiological, and epidemiological markers of illness as found in psychosis with onset in adulthood. Yet, it is often characterized by a more insidious illness onset, with higher frequencies of negative symptoms and thought disorders, more disorganized behaviour, more pre-morbid neurobiological and neuropsychological vulnerability indicators, more developmental delays, more comorbid nonpsychotic mental disorders, and a higher prevalence of familial diagnoses within the schizophrenia spectrum [1–3]. Since early onset schizophrenia-spectrum disorders often persist into adulthood, and treatment response and prognosis are less favourable in psychosis with early compared to adult onset [4], early-onset psychosis patients often face a long chronic course of illness.

In general, there is a rising awareness that childhood and adolescence is an important window of opportunity for early intervention in mental health [5]. Early onset psychosis is often associated with delayed detection and a mean duration of untreated psychosis of approximately 19 months, which may be associated with a hampered prognosis [6][7][3]. Furthermore, in patients with psychosis below age 18 years antipsychotic treatment is less efficient and associated with more adverse effects [4]. The incidence of schizophrenia spectrum disorders is increasing, as shown in a Danish study, with rates increasing approximately 25% for men and 40% for women in Denmark in the period from 2000 to 2012. This was mainly explained by a sharp and significant increase in incidence rate ratios among individuals below 24 years of age, due to a 2–3 fold increase in the youngest age groups [8]. A recent study found that 15% of all children and adolescents in Demark were diagnosed with a mental disorder before reaching 18 years of age. For schizophrenia spectrum

disorders the risk for girls was higher than boys (0.76% [95%CI, 0.72%-0.80%] vs 0.48% [95%CI, 0.39%-0.59%]) [9].

Outcomes in people with schizophrenia spectrum disorders are suboptimal with significant personal and societal costs [10], low quality of life and [11], low rate of recovery [12], substance misuse [13], higher rates of violence and legal problems [14–16], low educational and vocational attainment [17], and a significantly reduced life-expectancy of 15-20 years less than the general population [18–21]. Before chronicity and severe functional decline is manifest in adult early-phase psychosis, response to treatment is generally better [19]. Informal caregiving puts a large physical, social, and financial burden to the families of people with schizophrenia and have an impact on the relatives' mental health such as risk of depression, anxiety, and grief [22–27].

The above-mentioned factors document the burden of schizophrenia on patients, their families, the service system and the wider society, which implies a large economic societal burden especially due to lost productivity [26]. The economic impacts of psychosis go well beyond health care systems, with more than two-thirds of the costs falling outside of health care systems. The large burden to society has increased the focus on providing efficient treatment programs for early intervention.

In early-phase psychosis of young adults, clinical evidence strongly supports EIS [28], and the evidence base on cost-effectiveness of EIS for young adults is growing and support that extra investment in EIS generate value for money gains [29,30]. A recent meta-analytic comparison of EIS versus TAU by Correll et al. [6], which included 10 randomized controlled trials (RCTs) (n=2176 patients, mean age 27.5 years), demonstrated better outcomes for EIS patients on all clinical and organisational outcomes at all times (except for general and depressive symptoms at 18-24 months follow-up). However, no RCTs have tested this type of intervention in patient samples below the age of 18 years and a direct extrapolation from the results of the metanalysis to early-onset psychosis is difficult, since only a few percent of the participants in the meta-analysed studies were below age 18 years.

Complicating factors that can disrupt care and degrade functional outcome, might serve as modifiable targets for intervention especially relevant for youth. Such factors include school difficulties, academic failure or drop-out, co-morbid non-psychotic mental disorders and substance disorder, and poor coordinated transition to adult mental care services [31]. On the other hand, potential resilience factors specific for youth such as strong parent and family involvement, good

somatic health with few somatic comorbidities, involvement in school, less established misuse habits, more attention and available support from social services, and a greater neurobiological plasticity might represent possible avenues for increasing the chance for establishing interventions that work [32].

The overwhelming individual and socio-economic burdens of psychosis combined with the severe prognosis and increasing incidence of child and adolescent schizophrenia spectrum disorders, emphasize the lack of trials to direct clinical practice. Hence, there is an urgent need for evidence-based interventions that integrate psychosocial and pharmacological treatment while enforcing resilience factors in age-appropriate programs for psychosis with onset in individuals below age 18 years.

Aim

The study aims to compare the efficacy and cost-effectiveness of an Early Intervention Service (EIS) versus treatment as usual (TAU) in children and adolescents aged 12-17 years with first-episode psychosis.

Hypotheses

1. The EIS intervention (OPUS YOUNG) will be more effective than TAU in improving social functioning.
2. The EIS intervention (OPUS YOUNG) will be more effective than TAU in reducing positive and negative psychosis symptoms and provide a higher client satisfaction and health related quality of life.
3. The EIS intervention (OPUS YOUNG) will be more cost-effective than TAU.

Method and procedures

Design

The design is an investigator-initiated pragmatic, open label, parallel group, superiority RCT with blinded outcome assessment. No commercial interests will be involved. The trial will seek approval by the Regional Ethical Committee and by the Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark which assure that we comply with the General Data Protection Regulation according to guidelines of data collection in the Capital Region of Denmark and European Union standards. We will register the trial at clinicaltrials.gov. The trial procedures will

follow the Good Clinical Practice Guideline (GCP) [33] principles.

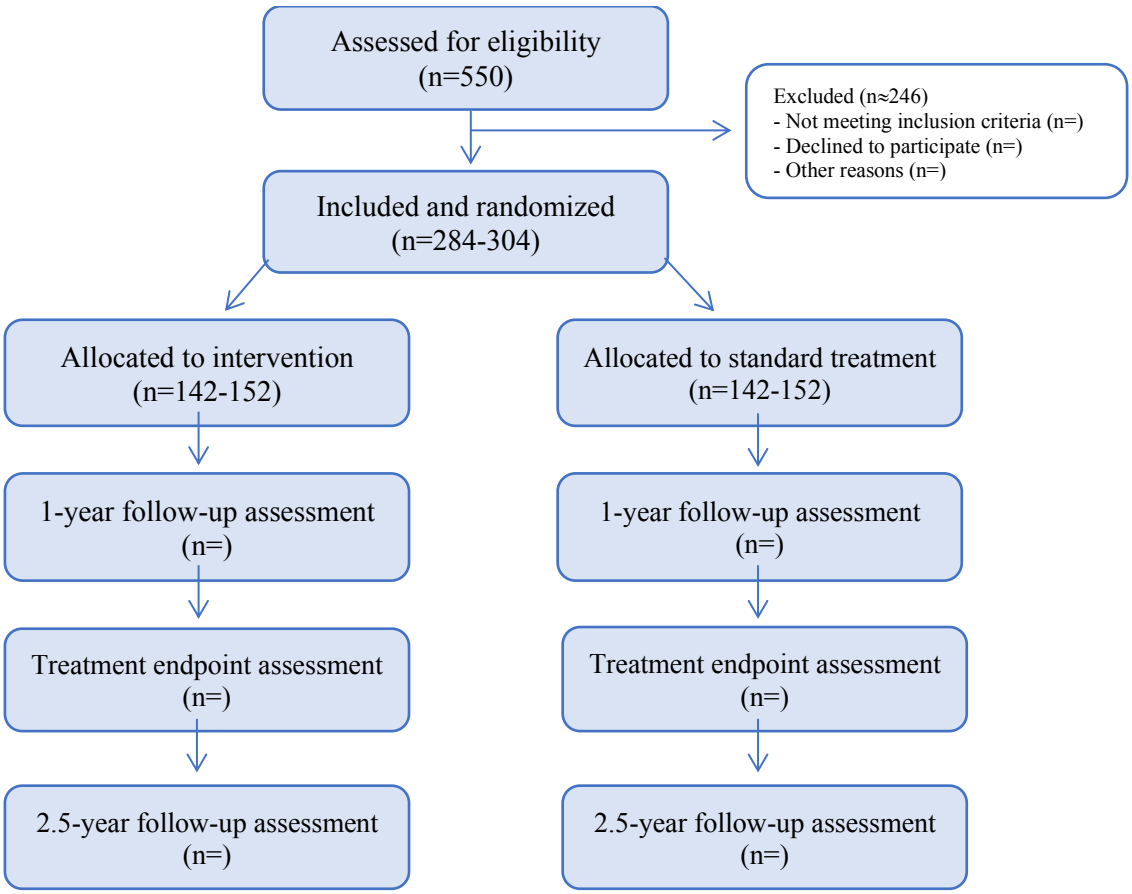
Participants, patient selection

Participants include children and adolescents (age 12-17 years, both inclusive) at the Child and Adolescent Mental Health Centre (CAMHC), Mental Health Services, Copenhagen University Hospitals, Capital Region of Denmark with a first-episode of psychosis fulfilling the ICD-10 [34] diagnostic criteria for schizophrenia or schizophrenia-like psychosis or depressive psychosis or substance induced psychosis.

Patients who meet the inclusion criteria during the inclusion period between June 2021 and September 2023 will be invited to participate in the trial and then randomized to either OPUS YOUNG intervention or TAU intervention.

Planned duration for study participation is two years from randomization to the treatment-endpoint at 24 months. We will perform an additional follow-up assessment 6 month after trial endpoint (see Figure 1 flow diagram and Table 2 study plan.

Figure 1 ***Flow of participants in OPUS YOUNG***



Patient inclusion criteria

1) Between 12 and 17 years of age (both inclusive) at trial inclusion.
2) First-episode psychosis within F2 spectrum (F20 schizophrenia, F21 Schizotypal disorder, F22 delusional disorder, F23 acute and transient psychotic disorders, F25 schizoaffective disorders, F28/29 other or un-specified non-organic psychosis) or depression with psychotic symptoms (F32.3, F33.3) or substance-induced psychosis (F1X.5) according to ICD-10.
3) Maximum 12 months since first prescription of antipsychotic treatment on the indication psychosis.
4) Speak and understand Danish.
5) Written informed consent from parents or legal caretakers. Participants who reach age 18 years during the trial will be asked to give personal written informed consent to continue their study participation.

Patient exclusion criteria

1) A diagnosis of mental retardation of at least moderate severity defined as an IQ of 49 or below (F71, F72, F73 according to the ICD-10).

2) Currently compulsory admission and/or treatment according to Danish legislation

Eligible patients who do not wish to participate

To be able to evaluate the external validity of the trial, we will register gender, age and diagnosis for the eligible patients who are not willing to sign informed consent and therefore not included despite fulfilling the inclusion criteria. We will register this information without the use of name or personal identification number and will only report this information on a group level.

Participant withdrawal

The informed consent to participate in the trial can be withdrawn by patients, parents, and legal caretakers at any time without any explanations.

Standard referral and clinical assessment of patients prior to study recruitment.

The Central Visitation Unit at Mental Health Services, Capital Region, and all in- and outpatient services at CAMHC refers all patients with suspected first-onset psychosis to a clinical assessment team within the CAMHC.

As part of the standard psychiatric assessment in the in- and outpatients services, the health care professionals in the clinics will conduct a comprehensive multidimensional assessment, including a

structured psychiatric diagnostic interview (K-SADS-PL and SCAN 2.1 (section 17, 18, 19)), with all referred patients with first-onset psychosis prior to the patients being invited to participate in the OPUS YOUNG-study.

In the CAMHS, there is a close collaboration between clinic and research. This means that health care professionals involved in the OPUS YOUNG-study are also engaged in the clinic. They assist with parts of the standard clinical assessments as clinicians in collaboration with the clinic. The results of the standard clinical assessment are reported to the patients' medical journal. Only the health care professionals involved in the standard psychiatric assessments and treatment in the clinics will have access to the patients' medical journal.

After standard clinical assessment has been conducted, the clinics as a standard have a clinical diagnostic conference in which the results of the assessments are concluded upon. If the consultant psychiatrist or specialized psychologist in the clinic find the patient eligible for the OPUS YOUNG-study according to the in- and exclusion criteria, the patient and parents/legal caretakers are informed that the OPUS YOUNG-trial is taking place at the CAMHS, and the family is asked whether they are interested in being informed about the trial.

Eligible participants, information about the trial, recruitment, informed consent, and screening.

If the eligible patient and the family is interested in receiving information about the trial, they will be invited to be informed about the OPUS YOUNG study by the OPUS YOUNG research team. If the patient and family upon receiving information are interested in trial participation, written informed consent will be obtained (including permission to access information from the patients' medical journal). The OPUS YOUNG research team will then, based on information from the standard clinical assessment in the medical journal, screen the participants for in- and exclusion criteria. If the patient fulfils the inclusion criteria 1-5 and none of the exclusion criteria, the patient will be included in the study.

Importantly, no research activities or data collection for research will be initiated prior to written informed consent has been obtained.

In some cases, it is more convenient for the patient and clinic to invite the patient to be informed about the OPUS YOUNG trial and invited to participate in the trial before the full standard clinical assessment (including K-SADS-PL and SCAN 2.1 (section 17, 18, 19)) has been completed in the clinic. Based on the clinical evaluation in the clinic, a patient with suspected or verified psychosis

can be asked by the clinic if they are interested in information about the OPUS YOUNG trial. If so, the clinic will facilitate an appointment with the OPUS YOUNG research team to meet the patient and family to inform about the study. If the patient and family wish to enter the study, the informed consent procedures described above will be conducted. In these cases, the standard clinical assessment performed in the clinic may not contain K-SADS-PL (full) and SCAN 2.1 (section 17, 18, 19), i.e. these assessments will then be performed after patient consent to participate in the trial (in that case, the data from K-SADS-PL and SCAN 2.1 (section 17, 18, 19) will be categorized as research data and will not be documented in the patients' medical journal). In these cases, the K-SADS-PL and SCAN 2.1 (section 17, 18, 19) functions as screening instruments, i.e., if the patient does not show psychotic symptoms or does not fulfil the inclusion diagnostic criteria for a psychotic disorder, the patient will not continue participation in the trial. Overall, the OPUS YOUNG research team will screen the participants for in- and exclusion criteria. If the patient fulfils the inclusion criteria 1-5 and none of the exclusion criteria, the patient will be included in the study.

Study assessments of included participants, parents/legal caretakers, clinicians, and municipal collaborators.

All included patients and their parents/legal caretakers participate in a baseline assessment. Some of the baseline data will be assessed by interviews or questionnaires, while others, such as the standard clinical interview, will be obtained from the patients' medical journal.

Table 1 shows the assessment schedule for the research baseline and follow-up assessments for patients and parents/legal caretaker. In total, outcome assessments will be conducted four times during the study period; at baseline (entry into the study), after 12 months, after 24 months (treatment endpoint), and after 30 months (follow-up assessment 6 months after treatment endpoint). Parents/legal caretakers will be assessed and included in the overall data collection. The research appointments (baseline, 12, 24 and 30 months) will be registered in the participant's medical journal, but no research data will be registered in the medical journal.

Clinician-rated working alliance will be assessed at 24 months. Clinicians and municipal collaborators will additionally be invited to participate in semi-structured interviews around the same timepoint. The interviews will focus on trans-sectorial collaboration and activities and will include demographic information such as professional background, age, sex and current employment and function.

Table 1 study assessment schedule							
Patient assessment			**Assessment time, months**				
Topic:	**Instrument/measure:**	**Adm***	**A***	**0**	**12**	**24**	**30**
Demographics	Demographic information	I		X	X	X	X
Duration of untreated psychosis	Interview based on IRAOS	I		X			
Primary and comorbid diagnoses	K-SADS-PL (full) SCAN 2.1 (section 17, 18, 19)	I	X		X	X	
Positive and negative symptoms	SAPS, SANS	I		X	X	X	X
Affective symptoms	YMRS HAM-D (6 items)	I		X	X	X	X
Global psychopathology	CGI-S, CGI-I	IR IR		X	X X	X X	X X
Social function	PSP	I		X	X	X	X
Intelligence	WISC-V (<16 years), WAIS-IV (≥16 years)	T	X				
Cognitive function	BACS	T		X		X	
Social cognition	Hinting Task + EIMT	T		X		X	
Quality of life	KIDSCREEN-10	Q		X	X	X	X
Quality-adjusted life year	CHU9D + EQ5D	Q		X		X	X
Self-efficacy (general)	GSE	Q		X	X	X	X
Working alliance	WAI	Q			X	X	X
Client satisfaction	CSQ	Q			X	X	
Negative effects of psych. treatment	NEQ	Q				X	
Trauma	Self-reported stressful life-events	Q		X			
Suicidal behaviour	Self-reported suicidal ideation and behaviour	I		X	X	X	X
School adherence	Days in school/education/employment (%)	R/I		X	X	X	X
Substance abuse	TEM	I		X	X	X	X
Somatic Health	Clinical assessment[1], laboratory tests[2], ECG	ME		X	X	X	X
Medication side-effects	UKU	I		X	X	X	X
Medication compliance	Self-reported use of antipsychotic medication	I		X	X	X	X
User perspectives on trans-sectorial activities	Semi-structured interview	I				X	
Assessment of parents or legal caretakers			**Assessment time, months**				
Topic:	**Instrument/measure:**	**Adm***	**A***	**0**	**12**	**24**	**30**
Parent information on child:							
Primary and comorbid diagnoses	K-SADS-PL (full)	I	X		X	X	
Executive functioning	BRIEF-2	Q		X		X	

Negative effects of psychological treatment	NEQ	Q				X	
School adherence	Days in school/education/employment (%)	Q		X	X	X	X
Duration of untreated psychosis	Duration of untreated psychosis (incl. patient referral process)	Q		X			
Genetic predispositions	Genetic predispositions	Q		X			
Information on parents/family:							
Demographics	Demographic information	Q		X	X	X	X
Parental Stress Scale	PSS	Q		X	X	X	X
Family Function	FAD	Q		X		X	X
Self-efficacy	GSE	Q		X	X	X	X
Client satisfaction	CSQ	Q			X	X	
User perspectives on trans-sectorial activities	Semi-structured interview	I				X	
Clinician assessment			**Assessment time, months**				
Topic:	**Instrument/measure:**	**Adm***	**A***	**0**	**12**	**24**	**30**
Working alliance	WAI					X	
User perspectives on trans-sectorial activities	Semi-structured interview	I				X	
Municipal collaborators			**Assessment time, months**				
Topic:	**Instrument/measure:**	**Adm***	**A***	**0**	**12**	**24**	**30**
User perspectives on trans-sectorial activities	Semi-structured interview	I				X	

*Notes: A** = Diagnostic and cognitive assessment prior to enrolment in the study conducted in the clinics. The results of these assessments will be obtained from the medical journal of the patients who consent to participate in the study and will be included as research data if informed consent is obtained.
*ADM** = Administration modus: I=interview, Q=questionnaire, R=registration, ME=will be obtained from the medical journal, IR= Interviewer-Rated.
Abbreviations = IRAOS: Instrument for the Assessment of Onset and Early Course of Schizophrenia [35]; K-SADS: Kiddie-Schedule for Affective Disorders and Schizophrenia[36]; SCAN 2.1: Schedules for Clinical Assessment in Neuropsychiatry [ref]; SAPS: Scale for Assessing Positive Symptoms[37]; SANS: Scale for Assessing Negative Symptoms[38]; YMRS: Young Mania Rating Scale; HAM-D (6 items): Hamilton Depression Scale[37, [40]]; CGI-S: The Clinical Global Impression Scale-severity[41]; CGI-I: The Clinical Global Impression Scale- improvement[42]; PSP: Personal and social performance scale[43]; WISC-V: Wechsler Intelligence Scale for Children, fifth edition or WAIS-IV: Wechsler Adult Intelligence Scale, fourth edition[44]; BACS: Brief Assessment of Cognition in Schizophrenia[45]; Hinting Task [46]; EIMT: Emotional Intensity Morphing Task[47,48]; KIDSCREEN-10: Health-related Quality of Life Screening Instrument for Children and Adolescents[49] ; CHU9D: Child Health Utility 9 Dimension[50]; EQ5D: European Quality of life - 5 Dimensions[51]; GSE: General Self – efficacy Scale[52]; WAI: Working Alliance Inventory scale[53]; CSQ: Client Satisfaction Questionnaire[54]; NEQ: Negative effects Questionnaire[55]; TEM: Trivsels- og Effekt Monitorerings-skemaet[56]; PSS: Parental Stress Scale [57]; FAD: The McMaster Family Assessment Device[58]; UKU: The UKU side effect rating scale [59]; BRIEF-2: Behaviour Rating Inventory of Executive Function, Second edition [60].
[1]Standard clinical somatic health examination includes blood pressure, pulse, weight, height, BMI, and abdominal circumference.
[2]Laboratory tests: Blood tests (fasting): triglycerides; total cholesterol; high-density and low-density lipoproteins; glucose; insulin; prolactin; haemoglobin; leukocyte cell and differential count; thrombocyte cell count; sodium; potassium; creatinine; aspartate amino transferase; alkaline phosphatases; thyroid stimulating hormone; vitamin D. Blood samples to analyse serum values of antipsychotics are drawn when needed. Urine tests: pregnancy test (at baseline and at follow-up if suspicion of pregnancy), screening for medication and substance abuse (at baseline and at follow-up if suspicion of substance use). ECG: electrocardiogram (standard leads).

Video and audio recording

Some of the research assessments (Hinting Task, PSP, and follow-up K-SADS with adolescents and parents) will be video or audio taped in order to secure and evaluate the data quality. Recordings will only be initiated if the participant and parents/legal caretaker have given permission to the recordings, and participation in the study is possible without having consented to video or audio recordings.

Registration of medication and use of health care during study

The use of antipsychotics and any other medication (drug, daily dosage, duration) and use of health care and social services (type and intensity) will be carefully recorded in both the experimental group and the TAU group. Information on medication use will be obtained through the participant's medical journal and by self-reported information at the assessment interviews. Information on service use will be obtained through the participant's medical journal as well as from the Danish Registers (see below).

Register-based information

Data on the patients will be extracted at 30 months (6 months follow-up after end-of-trial) from the following registers from Statistics Denmark: The Danish Population Register, the Danish Psychiatric Central Register, the Danish Education Register, the Danish Register of Special Education, the Danish Institution Register, the Danish Register of School Grades, the Danish Patient Register, the Danish Prescription Register, and the Danish Migration Register. We will assess socio-demographic information including school attendance, school grades and exams, labour market affiliation, civil status, cohabitation status, data on complications to the pregnancy and birth of the participant, education, living in an institution (and type of institution), use of any health care and social services and, in the unlikely event: cause of death.

Compensations

All participants, including parents/legal caretakers, will be offered the opportunity to be compensated for their transport cost.

Randomization

After baseline assessment the participants will be randomized 1:1 to either the experimental treatment (OPUS YOUNG intervention) or standard treatment (TAU). Randomization of the

participant will be centralised and computerised with concealed randomization sequence carried out by the database system used in the Capital Region of Denmark (REDCap) [61]. The randomization concealment mechanism is performed by a computer algorithm saved in REDCap [61]. Randomization cannot be influenced by persons, and block size will be unknown for investigators and clinicians. To optimize the comparability between treatment groups, randomization will be stratified by the two factors: *age* (12-14 years and 15-17 years) and for the main outcome, *PSP* (score 1-44 and score 45-100).

Blinding

A trial coordinator will inform the randomisation unit on the participants' data (age and identification) and will inform the patient and their family about which intervention programme he/she has been allocated to. The study is not blinded to patients, relatives, the OPUS YOUNG intervention team or staff members in TAU. The blinding applies to assessors (researchers) engaged with the outcome assessments and evaluation. In the follow-up outcome assessments, the patient is instructed in advance not to reveal what type of treatment he/she has received. If patients, despite instructions, reveal their treatment allocation to the researcher performing assessments, another person in the research group, who then will be kept blinded, will carry out the evaluation. The randomized intervention allocation is concealed until the statistical analyses of resulting data have been completed and conclusions drawn.

Table 2 Study Plan

	Preparation	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Start of study year	December 2019	June 2021	June 2022	June 2023	June 2024	June 2025
End of study year	May 2021	May 2022	May 2023	May 2024	May 2025	July 2026
Trial preparation (Fundraising, manuals)	From January 2019					
Recruitment of staff	From October 2019					
Preparation of OPUS YOUNG treatment including piloting the OY intervention	From December 2019					

Inclusion and randomization of participants to trial		First participant randomized July 2021		Last participant randomized September 2023		
Trial intervention		**X**	**X**	**X**	**X**	
Trial endpoint assessment (24- months follow-up)				First participant end of treatment July 2023		Last participant end of treatment September 2025
Follow-up assessment 6 months after trial endpoint (30 months follow-up)				First participant 6 months follow-up December 2023		Last participant 6 months follow-up March 2026
Data analysis, manuscript writing and publications						**X**

The OPUS YOUNG intervention and Treatment as Usual

The trial is pragmatic, comparing two years of EIS (OPUS YOUNG) to TAU. All the participants included in the trial are offered illness and age-appropriate treatment for two years. The OPUSYOUNG treatment and the TAU (described below) will be provided at three different geographical locations (OPUS YOUNG in a community environment, first in Brønshøj, later from fall 2023 in Glostrup) and TAU in a hospital setting) in order to prevent spill over effects between interventions, and to meet the EIS demand of a minimally stigmatizing community environment. The OPUS YOUNG treatment program will be manualized in order to function as a standard operational procedure for the intervention. The TAU follows the general recommendations and guidelines according to the clinical practice in the CAMHC.

Experimental intervention, OPUS YOUNG

The specialized coordinated OPUS YOUNG treatment is EIS based on a multidisciplinary team with a low caseload of a maximum of 1 staff: 10 patients in average, and assertive outreach and tailored case management. In OPUS YOUNG, Cognitive Behavioural Therapy (CBT) is a part of

the therapeutic framework of cognitive behavioural case management (CBCM). In CBCM, the case manager both takes care of general aspects of the patient needs and care and provide cognitive psychotherapy [62]. OPUS YOUNG treatment focuses on enhancing the patient's strengths and resilience, coping skills and resources, and will be tailored to meet the individual patient's needs. The approach of the OPUS YOUNG team and CBCM include sharing best available evidence when facing the task of making decisions, supporting the patients and their relatives in decision-making and considering their options and resources, and to help patients achieve personal preferences and maximize resilience by following the principles of shared decision-making [63]. "Experts by experiences" will be integrated in psychoeducation for patients, relatives, and as a regular part of the introduction program for new OPUS YOUNG staff members.

The OPUS YOUNG treatment consists of the following elements: modified assertive community treatment [64], cognitive-behavioural case management (CBCM) [62], psycho-educational family treatment including multiple family groups (MFG) [65] and psychoeducational siblings groups [66,67], Social Cognition and Interaction Training (SCIT) [68,69], possible individual Cognitive Behavioural Therapy (CBT) [62,70] in addition to CBCM, and manual based psychopharmacologic treatment building on (but not restricted to) the RAISE-ETP principles [71] and national guidelines [72].

To further meet known and common challenges for this age group, the OPUS YOUNG treatment has extra focus on components that strengthens resilience and are sensitive for achieving and maintaining positive benefits from the treatment: Special transition support, individual school/employment support, and prevention and treatment of substance abuse (further description of each element below).

The OPUS YOUNG team

Each OPUS YOUNG team is staffed by 1-2 specialist consultants in child- and adolescent psychiatry (one of the medical doctors may be a senior resident) and four to eight trained case managers (number of staff depends on number of patients included, however with a minimum of five staff members per team), who represent at least four different relevant professions (e.g. nurse, psychologist (preferably specialized in child- and adolescent psychiatry), pedagogue, vocational therapist, social worker).

All members of the OPUS YOUNG staff will be well educated, have profound experience with FEP and will be continuously trained and supervised in the core elements of the OPUS YOUNG treatment to provide the specialised assertive intervention. Team members must be trained in cognitive behavioural case management (CBCM) [62,73] and shared-decision making.

Cognitive Behavioural Case Management (CBCM)

All patients are designated to a primary staff member, a cognitive behavioural case manager (CBCM) (hereafter referred to as the case manager), who is responsible for the contact and alliance with both patient and parents/legal care takers and siblings throughout the two years of the OPUS YOUNG treatment. All staff members work as a case manager (except for the senior child- and adolescent psychiatrist consultant). In cooperation with a colleague, each staff member will be responsible for at least one of the group psychosocial programmes to support recovery (SCIT, psychoeducation to patients and parents/legal caretaker in MFGs, and sibling's psychoeducation groups).

CBCM comprises several components such as psychoeducation, case formulation, stress management, crisis management, challenging and behavioural strategies, and family work. CBCM offers patients a cognitive therapeutic approach with the aim to support autonomy, reduce stigma and to empower the individual in working towards personal recovery goals and illness self-management. All staff members are initially and on-going trained and supervised in CBCM [74] securing that all team members get a basic understanding of the cognitive principles, able them to include the basic cognitive therapeutic principles in their collaboration and working alliance with the patient and to strengthening their ability to complement and support patients participating in SCIT and individual CBT.

The case manager will give high priority to establishing and maintaining a strong and trustworthy alliance with the patient and his/her family, also when the patient is hesitant and/or reluctant towards the intervention and collaboration. The intensity of contact is flexible and phase specific. Typically, the patient and case-manager will initially be in contact weekly, however, the rate can be increased if needed and decreased if considered appropriate for the patients. The relationship between patient and case manager works consciously towards a strong working alliance [75,76], with confidence and transparency. It is essential for the case manager to be able to respond quickly, if changes in the patient's condition occur, which require increased support. Once a sustainable and trusting connection has been established, it is much easier for patient and his/her relatives to ask for

help and support in times of greater need. Appointments should match the patient's needs in general; meaning that the team offers a possibility for late afternoon appointments, the team is accessible in working hours and a possibility for patients and relatives to leave voice- or text messages outside working hours. The patient and his/her relatives can make direct contact with the case manager by cell phone. The patient and family should in advance be provided with a crisis plan comprising sufficient information to handle emergency situations and ability to access immediate help in the health care system when needed. This standard procedure will be developed as early as possible in cooperation with patients and relatives. Furthermore, the case manager is responsible for coordinating the treatment within the team, and for coordinating across school, social services, and other institutions involved in the treatment. The treatment is assertive, meaning that the team is responsible for maintaining contact with the patient and legal caretakers at all times. Meetings can be held in the patient's home or in other places in their community or at his/her case manager's office, according to the patient's preferences. The OPUS YOUNG intervention does not include a formal inpatient component. However, the case manager and team will ensure continuity of care by facilitating referral to inpatient units and may work with inpatient staff and directly with the patient if hospitalization is required.

Psychoeducational family-based intervention

Parents/legal care takers are usually the patient's closest relation and are thus very important collaborative partners as they have a unique knowledge of the patient and the family history. Psychoeducational family based intervention covers a program that provides families with education about psychotic disorders and related difficulties, and how to manage psychotic disorders, including strategies for problem-solving skills and how to improve communication within the family [77]. It has been demonstrated in several studies that family psychoeducation is associated with reduced rates of relapses [78,79]. The team invites the parents/legal caretakers to individual meetings from the very start of the treatment, to review the present situation and to create a working alliance, both for those who want to participate in psycho-educational Multi Family Groups (MFG) and for those who will not be able to join an MFG or refuse. Also, the team will invite and motivate all for participating in psychoeducational workshops. The parents/legal caretakers are offered on-going cooperation with the case manager and are invited to psycho-educational workshops, in which they are given formal information about the illness and how to manage it. Psychoeducation involves active interaction between the OPUS YOUNG team providing

the education and the family/relatives. In addition to individual psychoeducation, the team focuses on inviting and motivating patients and legal caretakers to participate in MFG [80,81], see below.

Psycho-educational multifamily groups (MFG)

Based on McFarlane's psycho-educational MFG [65], OPUS YOUNG will invite all patients and their parents/legal caretakers to participate in an MFG during a period of 12 months.

The MFG includes six to seven patients with their parents/legal caretakers and two trained group leaders. They will meet every second week for one and a half hour (a total of 20 sessions will thus be offered to each family). The groups will be scheduled in the afternoons, enabling participants to participate after school/work hours [65,81].

MFG address many of the complex and difficult every-day problems that families with an adolescent may face, in addition to more illness specific issues that most of the patients with psychosis are dealing with. MFG use principles of problem-solving techniques, which include all participants actively in the problem-solving process. In OPUS YOUNG the McFarlane's model of MFG will be age-adjusted to meet a younger population, by addressing questions and topics of relevance for this age group, e.g., how to manage school and peer relations or how to deal with misuse.

Sibling psycho-educational groups

As most of the adolescents experiencing FEP live and share their everyday life with their parents and siblings, siblings may experience increased levels of stress during the prodrome and onset of illness in their sister or brother, a burden affecting the whole family [82]. An explorative study of the experiences and needs of siblings of young adults with FEP treated in early intervention teams, found that siblings are greatly affected by the onset of the psychosis in their brother or sister, and although siblings did not identify themselves as caregivers, most of the siblings played a significant role in their brothers or sisters life [82]. The study conclude that the siblings desired a dynamic, robust and accessible service, e.g., information and support from peer siblings, to meet their needs [82]. Education and support for siblings will become increasingly important as they are both natural agents as caregivers now and in the future, also due to the familiar-high-risk for psychosis and mental illness it is important to reduce the level of stress in their everyday life [83]. A Cochrane review of psychoeducation for siblings of people with severe mental illness, find that siblings most often were recruited together with other family members, and that the overall proportion of siblings were low [66]. None of the studies in the review reported outcomes exclusively for siblings and the

authors were only able to include data from one small study in the review and thus, not able to conclude which type of psychoeducation were most effective in meeting siblings' needs [66].
In OPUS YOUNG all siblings from age 7 years (may be adjusted according to siblings needs and abilities) are offered participation in a siblings' psycho-education group matching their age or if this is not possible, individual psychoeducation will be offered. The psychoeducation will be dynamic and based on dialogue, include information on symptoms and how to cope and manages in their daily life as a sibling to a relative with a FEP. The siblings together with the OPUS YOUNG team and the family will determine whether the sibling's age-appropriate needs are best met by joining a siblings psycho-educational group or the psycho-educational family workshop [84] .

Social Cognition and Interaction Training (SCIT)
It is important for all people to be able to function socially, and the adolescent years are crucial for the development of independent social skills. A core characteristic in schizophrenia is impaired ability to function socially [85,86]. Impaired social functioning is obviously a problem that may stigmatize and marginalize children and adolescents with psychotic disorders, and in turn increase risk of social isolation and loneliness.

Furthermore, social functioning strongly predict poor long-term recovery [87–89]. Hence, implementing best practices for improving social cognition and functioning is an important clinical goal in EIS.
Social cognition is conceptualized as "the mental operations underlying social interactions, which include the human ability and capacity to perceive the intentions and dispositions of others" [90]. The impairments of social cognition in schizophrenia involve at least three broad domains: emotion perception, attributional style, and theory of mind (ToM) [68].

The SCIT program is the first coherent and comprehensive, stand-alone intervention targeting all three domains of social cognition. The SCIT program also targets underlying processes, such as cognitive rigidity, jumping to conclusions, and intolerance of ambiguity.

The SCIT has proven effective in adults with schizophrenia by improving patients' performances in key social cognitive abilities targeted by the program (emotion perception, social perception, ToM and attributional style) and by improving social relationships and overall social functioning [68,69]. In a feasibility study, the EPPIC group in Melbourne applied SCIT to early intervention treatment. The participants were aged between 16 and 26 years. SCIT was well tolerated, and retention was

good. The participants improved significantly on measures of emotion recognition and social and occupational functioning. As a result of the study's findings, the EPPIC group suggests applying SCIT early in the course of illness. The group argues that SCIT would prove especially efficacious if applied as early as possible in the course of illness due to greater brain plasticity in the adolescent brain development. Also, the SCIT appeared acceptable for a young population [91].
SCIT is a manual based group intervention including 20 sessions, 1 session/week, with each session lasting 60 min. SCIT is comprised of three phases:
(1) emotion recognition training while considering social context (defining emotions, emotion mimicry training, understanding paranoia)
(2) recognizing attributional styles and 'figuring out situations' (distinguishing facts from guesses, jumping to conclusions, understanding bad events)
(3) integration of these skills into real-life situations [68,92,93]

The SCIT program uses a variety of supporting materials and activities like games and videos to teach the pitfalls of jumping to conclusions, improve cognitive flexibility in social situations, and help participants distinguish between social "facts" and "guesses". The activities are engaging as they resemble youths' leisure activities. The original SCIT materials will be adapted to fit Danish children and adolescents. In the third phase, integration, the participants are helped to put into practice what they have learned. To prepare for real-life situations, new understandings and skills are rehearsed through role-playing sessions together with the therapist or with other participants in the group.

Cognitive Behavioural Therapy (CBT)
Individual cognitive behavioural therapy (CBT) is recommended for first-episode psychosis as well as for patients with schizophrenia [93], even though the evidence is questionable. Two recent meta-analyses of CBT for adults with psychosis or schizophrenia found effects "in the small range" on overall symptoms [94] and functioning [95]. However, the benefits were not sustained after end-of-trial, and no robust effects were found with regard to psychotic symptoms, distress or quality of life. This was particularly the case when adjusting for lack of masking and other potential biases.

A systematic review of psychological interventions in psychosis for children and adolescents identified only one small study of CBT (a feasibility RCT, n=20) providing some indications that psychological interventions might be effective in early onset psychosis [96].

Still, CBT was offered in 7 out of 10 EIS programs recently reviewed [6], typically with the aim to support autonomy, reduce stigma and empower the individual to work towards personal recovery goals and illness self-management [97]. In OPUS YOUNG these aims are targeted by the core components, particularly the cognitive-behavioural case management (CBCM) and the SCIT in combination.

In order to avoid stacking of psychosocial treatment elements with the risk of overwhelming the participant, we will reserve the possibility of standard individual CBT to those patients in need of intensified psychological treatment. CBT would aim to 1) reduce the burden of *non-psychotic symptoms* (anxiety, depressive symptoms, reactions to trauma, substance abuse); and to 2) improve social relationships, enhance positive activities and feelings, and thereby improve self-esteem and install hope for the future.

The CBT will be provided by the team psychologist (or psychiatrist), who will have formal training in CBT and a thorough clinical experience with CBT for youths.

Pharmacological treatments

The pharmacological treatments are manualized and based on international and Danish guidelines [72,98,99], which recommend a low-dose strategy for patients with FEP. This recommendation is supported be recent findings of increased risk of death (with a 4.3-fold increased risk of death from cardiovascular or metabolic causes) in children and youth treated with antipsychotic doses above 50 mg chlorpromazine equivalents compared to children and youth treated with antipsychotic doses below 50 mg chlorpromazine equivalents (for which there was no significantly increased risk) [99]. Guidelines furthermore include restriction to indications for which there is good evidence of efficacy, adequate trial of alternatives including psychosocial interventions, when possible, cardiometabolic assessment before treatment and monitoring after treatment, and limiting therapy to the lowest dose and shortest duration possible. The pharmacological treatment in OPUS YOUNG will adhere to evidenced based use of second-generation antipsychotic drugs as the first choice and will at all times strive to avoid off-label use as much as possible. Due to the overall equality in efficacy among antipsychotic drugs used in adolescent FEP, the choice between available antipsychotics should be guided according to evidence base, approval status and side effect profiles, which differ [100,101]. An algorithm for selecting an appropriate antipsychotic agent will be

provided in the manual (see Appendix 1). The manual based psychopharmacologic treatment will build on the RAISE-ETP principles [71]. Systematic and close monitoring of side effects such as sedation, extrapyramidal symptoms, prolactin increase, QT prolongation, and weight gain, increased waist circumference, lipid and blood glucose abnormalities indicating risk factors for cardiovascular diseases and diabetes with validated scales [59]; are mandatory, as well as actions to manage side effects individually. The treatment follows a shared decision-making model involving the legal caretakers when appropriate and the patient must see the prescriber on a regular basis according to individual needs.

The pharmacological treatment in OPUS YOUNG is described in a separate manual and algorithm which together with the OPUS YOUNG protocol [Protocol version 2, dated September 9, 2020] has been presented to the Danish Medicines Agency (DMA), case number 2020091477. The Danish Medicines Agency has concluded (September 18, 2020), that the OPUS YOUNG trial is not covered by the definition of a clinical (medicinal) trial, since the aim of the study is not to investigate the pharmacological effect of each of the drugs, but rather to test the effect of the algorithm. The DMA therefore concluded that the study should not seek approval in DMA but should seek approval in the Scientific Ethical Committee. The DMA furthermore recommends contacting the Danish Data Protection Agency concerning registration and further handling of personal information in the study. Finally, the DMA asks the study group to be vigilant concerning reporting to the DMA of spontaneous side effects to medications (see guidelines, https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-of-medicines/report-a-side-effect/humans/report-an-adverse-drug-reaction-from-medicines-for-healthcare-professionals-e-form/). We will promote side effect reporting to the DMA according to these guidelines.

Special components of OPUS YOUNG

The OPUS YOUNG team has special focus on areas particularly critical for this group of adolescents:

1) *Special transition support* will bridge the gap between child and adolescent psychiatry and adult psychiatry, or social care, by securing the patients a safe transfer from OPUS YOUNG treatment to continued standard treatment in child and adolescent or adult mental health services (depending on age at end of the two years OPUS YOUNG treatment). In contrast to standard care, patients in OPUS YOUNG will not be terminated from the intervention and transferred to adult psychiatry if they turn 18 years of age during the two years intervention

period. The OPUS YOUNG team will follow the principles of the "NICE guidelines for supporting young people in their transition to adult services" [31] . Principles in the NICE guidance, emphasizes to allocate a named worker (in OPUS YOUNG; the case manager) to oversee, coordinate and delivery transition support and advocate for the young person if needed, and further, to ensure that the overall plan for supporting is revised if the young person is not in contact with services after transfer [31]. The transition to standard care will be scheduled approximately half a year in advance.

2) *Individual school/employment support.* In cooperation with the patients' school or educational/vocational institution, the case manager will support and encourage educational and vocational goals among all adolescents, including those who have dropped out of school or are at risk of doing so. To ensure that relevant education/vocation is provided, we will liaise with the patients' school and educational authority and with their parents. Mutual agreement determines whether a special educational needs' assessment is necessary. The case manager and the team will, in corporation with extern agents provide supported employment programs for those above compulsory school age who wish to find employment [102]. Case manager and the team will consider and motivate for other work‐related activities or supported work when individuals are unable to attain a regular job or are unsuccessful in their attempts to find employment. To enable the patients' access to employment and educational opportunities, these efforts will be sensitive to the young person's needs and skill level and will be worked out in partnership with local stakeholders. OPUS YOUNG will follow the principles of the NICE guidelines for education, employment and occupational activities for children and young people with psychosis and schizophrenia [103].

3) *Prevention and treatment of substance abuse* are integrated in the OPUS YOUNG intervention and carried out by the case manager in collaboration with, and supervised by, consulting experts. A Cochrane review of psychosocial interventions for cannabis use disorder suggested that improvements in cannabis use, frequency and severity of dependence were most likely when the treatment offered were a combination of cognitive behavioral therapy (CBT) and motivational enhancement therapy (MET) [104]. This combination of CBT and MET as well as the use of gift cards and follow up sessions, have in a Danish randomized study shown to be very effectful in reducing and cessation of cannabis use among young people [105,106]. In

OPUS YOUNG we integrate this combination of CBT and MET as add on of 12 manualized sessions for those patients who have a misuse and who are motivated for treatment, with use the MOVE manual [107].

In general, and to ensure confidence and the opportunity to collaborate with the patient on minimization or cessation of misuse, the case manager will exercise a non-judgmental approach towards use of substances. OPUS YOUNG will follow the principles of NICE "Coexisting severe mental illness and substance misuse: assessment and management in healthcare settings" and consider the expected NICE guideline "Drug misuse prevention" [108].
We will also actively intervene to prevent initiation of smoking and promote smoking cessation, as this poses an additional severe threat to health [109]. From our prior studies including youth with psychosis, we know that tobacco use is high among these patients. In the TEA trial, 40% of 12-17 year old patients with early onset psychosis compared to 1% of healthy controls were smokers ($p<0.001$) [110].

Experts by experience

In OPUS YOUNG the use of "experts by experiences" also known as peer support, will be integrated as an independent and permanent part in psychoeducation for both patients, caregivers, and siblings. Furthermore, experts by experiences will contribute to the introduction of new team members and act as an expert panel like the OPUS panel. The OPUS panel was founded in 2009 by a group of young people who had been in treatment in EIS teams (OPUS) in Denmark and their relatives. The purpose of the panel is that the members with their personal history and through dissemination about living with an invisible disease helps to broaden the knowledge about the diagnosis of schizophrenia, and reduce the stigmatization experienced by both patients and therapists in the field. In addition, experts by experiences will increase the hope for current patients treated in EIS and affect the treatment culture in a positive direction. An early intervention youth mental health service in Melbourne uses families as partners in mental health care in close collaboration with clinical teams to provide new family members with a range of interventions to assist recovery, their experience that new families asked for contact with peer-families very early in the course of treatment [111].

A phase-specific individual tailored treatments course in OPUS YOUNG

OPUS YOUNG treatment is a complex intervention that allows to be tailored to the individual patient. Therefore, many different courses of treatment can take form. Table 3 shows an example of how the two years intervention could proceed.

Table 3 Example of OPUS YOUNG treatment for two years

Example of 2-years OPUS YOUNG treatment

Year	1	1	1	1	2	2	2	2
Cognitive Behavioural Case Management (CBCM)								
Collaboration with relatives								
Social Cognition and Interaction Training (SCIT)								
Multi Family Groups (MFG)								
Individual Cognitive Behavioural Therapy (CBT)								
Pharmacological treatment								
Individual school/employment support								
Prevention and treatment of substance abuse								
Transition support								

Mandatory for all patients

When motivated and able, flexible start time

A motivated option

According to individual needs

Treatment as usual (TAU)

Participants allocated to the standard treatment will be offered the existing treatment in CAMHS. According to the Specialty Plan for child and adolescent psychiatry by the Danish Health Authorities, 2019 [112] children and adolescents with psychosis will be referred to a predefined level of care in the Danish health care system according to the severity and complexity of their psychotic illness. In essence, the individual patient will be referred to the unit in CAMHC that best fits the level of care indicated. In Denmark, three levels of care may be provided: *Main function, regional function, or highly specialized function*. If the needs of a patient change during the course of illness, the patient will be transferred to a higher or lower level of care. The treatment follows national Danish guidelines and local guidelines but is not manualized. None of the levels of care in TAU are currently assertive as a standard. The unit for highly specialized function for children and adolescents with schizophrenia in CAMHC manages the patients with the most severe psychotic illness. In addition to standard treatment, this unit is specialized by providing a multidisciplinary team, case-management (no defined upper case-load), family support and psychoeducation, in addition to psychopharmacological treatment. In some cases, social skills training and CBT may be offered. In general, office visits take place in outpatient clinics. The main and regional functions are

both at a less intensive level of care than the highly specialized function, and standard treatment usually offers psychoeducation, antipsychotic treatment, and some support to the families. The outpatient units proving the TAU plans to implement an adjusted and transdiagnostic version of flexible assertive community treatment (F-ACT) building on reports from Danish adult mental health services [113] and models from Dutch youth mental health services [114]. The establishment of F-ACT teams in TAU are expected to be initiated in September 2021.

Fidelity monitoring

We will assess the fidelity of the OPUS YOUNG treatment and structure during the trial period, using an special OPUS YOUNG modified version (Appendix 2) of The Danish Fidelity Scale for Specialized Early Intervention Team [115–117]. To lower the possibility of idiosyncratic judgement, two assessors will independently conduct the fidelity assessment once a year, and their interrater reliability will be measured. Further we will assess fidelity of core parts of the treatment; CBCM, SCIT and Family intervention to guide and maintain adherence to the OY intervention throughout the trial period. Furthermore, meetings and co-rating will be arranged to ensure program fidelity and interrater reliability.

Recruitment of staff, training, and preparation of OPUS YOUNG treatment

Since January 2019 an OPUS YOUNG manual including all treatment elements suiting the target group has been developed. The first OPUS YOUNG team has been established, and they have tested the OPUS YOUNG intervention since January 2020. The team has participated in the final preparations of materials and are qualified and educated in the manual-based OPUS YOUNG treatment, and ready for including patients by June 2021. The first team will be on-going throughout the entire trial period and will get an important status as a critical mass that can help with the introduction of the new team members and guide their education in the manual-based treatment. Recruitment of additional multidisciplinary staff will take place gradually relative to the number of patients included in the experimental treatment (see figure 2).

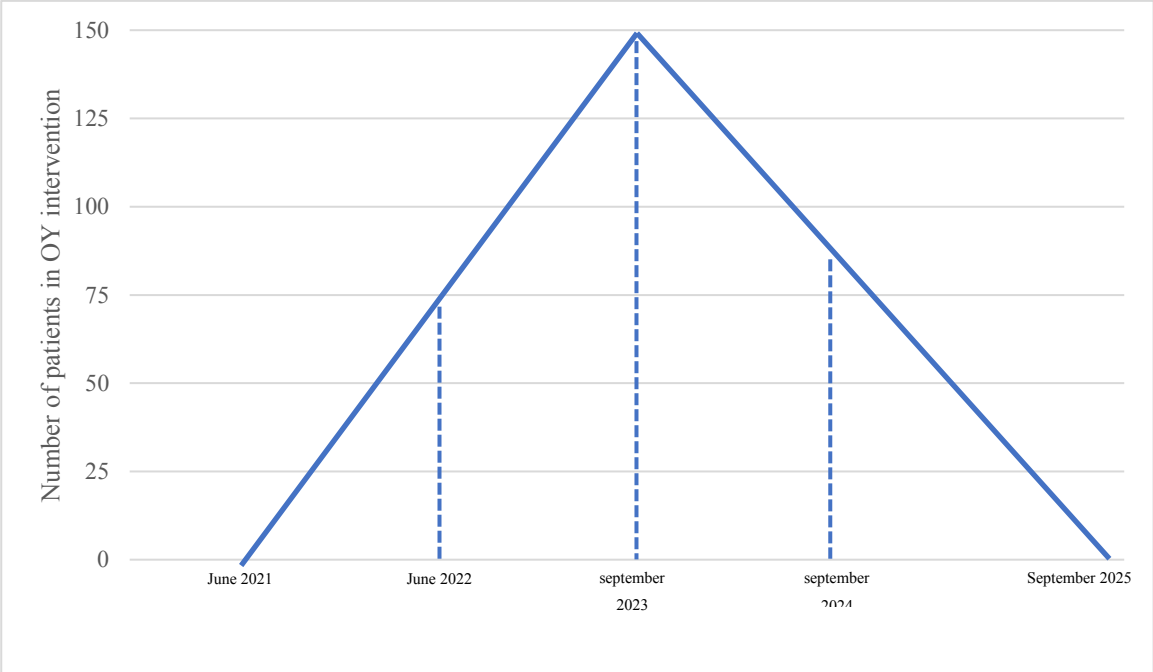
The OPUS YOUNG staff will in addition to their clinical profession be educated and trained in cognitive behavioural therapy as well as the core elements of the OPUS YOUNG treatment: CBCM, MFG, SCIT, MOVE, and the psychoeducational family-based involvement. Moreover, training of staff will include: the overall program principles of early intervention services, psychopathology and how to work together as a team of health professionals with different and

overlapping roles. Ongoing training and supervision will ensure that the staff is qualified to perform the core elements of the treatment. The OPUS YOUNG team will develop material and videos for use in the SCIT-treatment.

Cooperation with the OPUS organization for adults

The OPUS YOUNG team will have close collaboration with the Danish OPUS teams for adults aged 18-35 years and benefit from their 20 years of experience and competence in EIS.
Experts from the OPUS team together with experts in cognitive behavioural therapy, will initially and on-going, train, teach and supervise the OPUS YOUNG staff in the function as CBCM. Likewise, experienced multifamily group-therapists from the OPUS team will teach and supervise OPUS YOUNG staff in how to lead and facilitate a multifamily-group. OPUS YOUNG team leaders will attend the OPUS-leader meetings, which again will facilitate cooperation, increase the possibility for knowledge to be shared and developed between teams and bridge the age spread. The OPUS YOUNG staff will participate in the annual national OPUS conferences. A close collaborating will strengthen the overall specialized early intervention efforts for young people with the first episode of psychosis in Denmark.

Figure 2 Expected number of patients in OPUS YOUNG intervention during the 26 months of recruitment. OPUS treatment team 1 will be engaged from June 2021 to September 2025. OPUS treatment team 2 will be engaged in the expected two-year period when the patient volume is above 71 patients.



Hierarchy of outcome measures

Primary outcome

The primary outcome is change in the estimate of the adolescent's social function, measured with Personal and Social Performance Scale (PSP) [43]. PSP provides a global score on a scale from 1-100, with lower scores indicating lower social functioning, as well as scores on four subdomains (Socially useful activities, Personal and social relationships, Self-care, and Disturbing and aggressive behaviour) on a scale 6-point Likert scale. The scoring of PSP is based on all available information and concerns the patient's daily level of functioning in the family, in school, and during leisure time during the past month. Researchers will interview the participants prior to the scoring of PSP using a semi structured interview guide suitable for children and adolescents, developed by the OPUS YOUNG research team. The final PSP-score will be determined using consensus rating, by which the rater will discuss the PSP score with an experienced user of PSP (the co-PI of the OPUS YOUNG study) and/or a senior consultant and other researchers from the research team. Prior to the initiating the OPUS YOUNG study, we will conduct a pilot-study to ensure that the assessors have a high level of inter-rater reliability with ICC values for the primary outcome measure of at least 0.70, prior to working as assessors in the trial (ICC is calculated in SPSS using two-way mixed models for absolute agreement on single measures). Assessors at entry and at the follow-up interviews will be independent and blind to treatment allocation. Patients will be instructed to maximize efforts to keep their treatment allocation unknown for the investigator.

Secondary outcome measures: Positive symptoms, negative symptoms, and disorganized symptoms (SAPS and SANS); client satisfaction (CSQ); and quality of life (KIDSCREEN-10).

Exploratory outcomes:
Affective symptoms (YMRS, HAM-6); global psychopathology (CGI-S, CGI-I); duration of untreated psychosis (IRAOS); global cognitive functioning (BACS total score); social cognition (Hinting Task and EIMT); general self-efficacy (GSE); patient and clinician rated treatment alliance (WAI); negative effects of psychological treatment (NEQ); school adherence; parental stress (PSS); family function (FAD); quality-adjusted life year (CHU9D and EQ5D); executive functioning (BRIEF); socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviours (PSP subscales); use of psychopharmacological treatment; substance abuse; and the use of psychiatric and social services.

Sample size calculation
Based on the literature concerning the level of psychosocial dysfunction measured with PSP in early onset psychosis (EOP) [118–121] we expect a Standard Deviation (SD) on PSP around SD=13. Concerning the expectations on relevant group difference in improvement during two years of EIS [6,122] we have evaluated the minimal relevant difference (MIREDIF). MIREDIF should represent a meaningful minimal group difference in response in the sense that it would justify a choice between two interventions in a clinical setting. The total PSP scale score range from 1 to 100. The metanalysis [6] on EIS interventions found, for functional outcome measured with Global Assessment of Functioning (GAF, scaled 1-100) including n=1005 participants in 7 studies, a standardized mean difference (difference in mean outcome between groups/standard deviation in outcome among participants) of 0.21 (in the individual 7 studies included ranging from 0.02 to 0.56). With a SD of 13, this equals an expected difference in PSP scores between groups of around 2.73, ranging from 0.26 to 7.28. Based on these findings and the evaluation of what is clinically meaningful when regarding the PSP 10-point ranges of functioning we have decided that it would be clinically relevant to be able to detect a difference of 5 points in outcome score on the total PSP scale between the two interventions. Using a power of 90% and a two-sided alpha of 5%, and expecting a SD of 13 on PSP, the required sample size necessary to detect or reject a difference of at least 5 points between the OPUS YOUNG and TAU group on PSP at endpoint is 284, why we

plan to enrol a minimum of 142 patients in each group. However, to account for drop-outs and due to our relatively long recruitment procedure time, where patients are referred from the clinic and may wait during the assessment period being offered participation, we will include up to 152 patients in each group if necessary, within the recruitment period. This will ensure that patients who are in the recruitment process will still be offered participation in the study even if the minimum of 284 participants has already been enrolled. This is ethically more proper, as patients in the centre entering the recruitment procedure are informed about the potential possibility to be offered inclusion in the study. The last patients will be assessed and included by September 1st, 2023. After this, no more patients will be included.

The required sample size was estimated as follows (N=total sample size, SD=standard deviation of the outcome measure, α=type 1 error, β=type 2 error, MIREDIF=minimal relevant difference of outcome measure, z = fractiles in normal distribution), when assuming equal sample sizes, equal SDs for the two interventions, and α=0.05 and β=0.10:

$$N = 4 \times (z_{1-\alpha/2} + z_{1-\beta})^2 \times (\frac{SD_1}{MIREDIF})^2$$

The required sample size with an estimated SD of 13 and a MIREDIF of 5:

$$N = 42 \times (\frac{13}{5})^2 = 284$$

Handling of study drop-out:

Based on data from a prior study (the TEA trial) of 113 patients with first-episode psychosis aged 12-17 years conducted in our CAMHS in the period 2010-2014 we have evaluated the expected study drop-out in the OPUS YOUNG trial. The TEA trial compared the beneficial and harmful effects of two antipsychotics, aripiprazole versus quetiapine, in a 12-week study. The drop-out rate (lost to follow-up assessments at week-2, week-4 or week-12) was 14% and 10%, respectively. In the TEA trial missing data was handled by intention-to-treat-analysis and multiple imputations [123]. In the OPUS YOUNG study, including an identical group of participants, we expect a drop-out rate of approximately 10%. We expect that the combination of pharmacological and psychosocial treatment in both intervention arms will motivate the patient and family to adhere to treatment. Furthermore, even though the drop-out rate for the two-year adult OPUS study was approximately 30%, our experience from the clinic is that parents intensively support young patients to adhere to treatment and support continued participation in clinical trials.

As we scientifically and ethically find it important to strive to include the most exact needed number of participants possible, not too few (risk of loss of statistical power), not to many (risk of burdening too many patients with engagement in a RCT) we will handle missing data as a result of study drop-out by performing intention-to-treat analysis with multiple imputation of missing data [124]. See also section on statistical analysis below.

Power calculation for secondary outcome measures

For secondary outcomes, we have performed power calculations on the most relevant secondary outcome measures. Based on the results of the power calculations the measures SAPS, SANS, CSQ, and KIDSCREEN-10, were selected as secondary outcomes.

SAPS, SANS

We are planning a trial with a minimum of 284 participants randomized 1:1. In a previous study, the response within each intervention group was normally distributed with a SD of 1.4 (SAPS) and 1.2 (SANS) points. If the true difference in the experimental group (OPUS YOUNG) and control group (TAU) for both SAPS and SANS is a mean of 0.4 points [125] with a standard deviation of 1.4/1.2 points, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 80%. The type I error probability associated with this test of this null hypothesis is 5%.

CSQ

We are planning a trial with a minimum of 284 participants randomised 1:1. In a previous study the response within each intervention group was normally distributed with an SD of 4.45 points. If the true difference in the experimental group (OPUS YOUNG) and control group (TAU) is a mean of 3.09 points [125] with a standard deviation of 4.45 points, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 99%. The type I error probability associated with this test of this null hypothesis is 5%.

KIDSCREEN-10

We are planning a trial with a minimum of 284 participants randomised 1:1. If the true difference in the experimental group (OPUS YOUNG) and control group (TAU) is a mean of 5 points and with

an expected standard deviation of 10 points [126], we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 99%. The type I error probability associated with this test of this null hypothesis is 5%.

Table 4 Power calculation

OUTCOME	MIREDIF	SD	N	Power
Primary				
PSP	5.0	13	2*142	90%
Secondary				
SAPS	0.4	1.2	2*142	80%
SANS	0.4	1.2	2*142	80%
CSQ	3.09	4.45	2*142	99%
KIDSCREEN-10	5	10	2*142	99%

Notes: Minimal relevant difference of outcome measure (MIREDIF), Standard Derivation (SD), Number of cases (N)

Evaluation of cost-effectiveness of OPUS YOUNG

The majority of first episodes of psychosis occur in adolescence or young adulthood, and it is important to detect and treat these early as delayed treatments can lead to poor clinical and social outcomes, with potential consequences over the lifetime for the individual and the society. Despite increased implementation costs, investments in EIS for young adults have shown to be cost-effective in OPUS due to lower psychiatric health care costs and better outcome [30]. To assess the cost-effectiveness of the OPUS YOUNG intervention, we will conduct an economic evaluation of the trial adopting a public-sector perspective. The cost-effectiveness analysis compares differences in costs and outcome between the intervention group and standard treatment by calculating the incremental cost-effectiveness ratio [127]. The time horizon of the economic evaluation will be 2.5 years. Outcome measures and cost data will be based on collected research and clinical data combined with register data [30].

Evaluation of psycho-educative siblings' groups

In a qualitative-design we will explore siblings' perceptions of being a sibling to a brother or sister with a FEP and identify factors important for siblings to benefit from the psycho-educative siblings' group. We will invite siblings to participate in an individual, semi-structured interview exploring

their experiences of being siblings to a brother or sister with FEP using a descriptive phenomenological approach to gain an in-depth understanding of the lived experiences of siblings.

Data-management

The assessors will enter data directly into a database REDCap via an online Case Report Form (CRF). A data manager will ensure that all variables are properly defined with variable and value labels. Algorithms will be kept in special files. Data will be exported to relevant software packages: (SPSS, SAS, Stata, R.). All data will be examined carefully in order to identify errors in data entry.

Statistical analyses

The analyses will be according to intention-to-treat with two-sided tests. Missing data will be handled by multiple imputations. The primary outcome measure, as other continuous outcome measures, will be analysed with mixed model analysis with repeated measurements with unstructured variance matrix, using the mixed model command in SPSS. This approach assumes that the distribution of missing data can be estimated from the information from previous assessments and from information about other participant cases in the database. The condition for using this method is the assumption that data are missing at random or missing completely at random when taking into consideration the information extracted from baseline assessments and information about the other participants in the database. In this model, baseline values of the scales are included. All tests will be two-tailed. The threshold for the significance level will be set at $p<0.05$. For evaluation of the dichotomous outcome measures, we will use multiple multivariate imputations, using all other covariates to impute a distribution of missing values. The dichotomous outcomes will be analysed with logistic regression analyses. Variables included as covariates will be the same as those included in analyses of continuous measures. Similar to the repeated measurement, the condition for using multiple imputations requires that data are missing at random or missing completely at random, when taking into consideration the information extracted from baseline interviews and information about the other patients in the database. Analysis will be based on intention-to-treat principles. Data from all patients will be included in the group to which random assignment is made, regardless of intervention received.

The specific hypotheses examined are:

- *The primary hypothesis:* 2 years OPUS YOUNG is superior to 2 years TAU (CAMHS or CAMHS+AMHS) examined in all patients aged 12.00 to 17.99 years at inclusion.
- *Planned sensitivity analysis 1*: 1-year OPUS YOUNG vs. 1-year TAU CAMHS in patients ages 12.00 to 16.99 years at inclusion (hence, the patients in this study sample do not turn 18 years during the trial and are solely treated in CAMHS).
- *Planned sensitivity analysis 2:* 2-years OPUS YOUNG vs. 2-years TAU CAMHS in patients aged 12.00 to 15.99 years at inclusion (hence, the patients in this study sample do not turn 18 years during the trial and are solely treated in CAMHS for the entire intervention period of 2 years).
- *Planned sensitivity analysis 3:* 2-years OPUS YOUNG vs. 2-years TAU CAMHS + AMHS in patients aged 17.00 to 17.99 years at inclusion (hence, all patients in the TAU group will have undergone transition from CAMHS to AMHS, while the patients in the OPUS YOUNG group will receive OPUS YOUNG treatment for the entire 2 years of intervention.

Due to expected lower sample size in the three planned sensitivity analysis, we do not aim to show statistical superiority of OPUS YOUNG over TAU in these analyses but will examine possible differences by comparing effect sizes.

Ethical considerations

Both the patients and parents/caretaker may be in a state of psychological crisis at the time they are invited to participate in the trial, making it difficult for them to decide whether to participate in the study. There is a risk that they will consider OPUS YOUNG better than TAU, which may affect them when the outcome of randomization is revealed. Still, we do not expect anyone to be affected negatively from being involved in the trial. While OPUS YOUNG is geographically located in a civilian environment, there is still a risk that some participants will find being in OPUS YOUNG treatment associated with stigmatization.

In general, the results of this trial can be of great importance for future health-care planning to benefit young people with a first-episode psychosis. OPUS YOUNG treatment is tailored to meet the patient's individual needs and to support the patient's empowerment and recovery process.

Written informed consent

All participants are below 18 years of age when invited to participate in the trial, why signed informed consent will be obtained from parents/legal caretakers prior to entering the trial. The adolescents between 15 and 17 years of age will sign written informed consent in addition to the parental consent. Municipal collaborators and clinicians who wish to participate in the interviews regarding user perspectives on trans-sectorial activities will also sign written consent before the interview.

Procedures regarding verbal and written information:
Patients, who are deemed eligible to participate in the trial according to the in- and exclusion criteria, as well as their parents/legal caretaker, will be given verbal information about the trial by a health care professional involved in the trial. The verbal information will be provided during regular clinic visits at the CAMHS in the presence of parents/legal caretakers, and in the privacy of an examination room, together with the patient's primary health care provider. The verbal information will be provided in an age-appropriate manner and parents/legal caretakers will be explained their right to have an assessor (e.g., friend or family member) present and in case the parent/legal caretaker should want that, a new appointment will be made for the information meeting. Written information brochures explaining the study background, procedures, aims, and (patient) rights will be provided both to the participant (age-adjusted language for the 12-14 years old and the 15-17 years old, respectively) and the parents/legal caretakers. Both the verbal and written information will inform about participants' rights to withdraw from the trial at any point without it affecting future treatment.
Potential participants and their parents/legal caretakers will have a minimum of 24 hours to consider participation before being contacted by the health professional involved in the trial. The child and their parents/legal caretaker will be informed that the decision must be a shared decision, and both the child as well as their parents/legal caretakers should agree on the child's participation prior to the parents/legal caretakers' consent to the participation. If potential participants and their parents/legal caretakers approve to participate, parents/legal caretakers and the participating youth if 15 years of age or above will sign informed consent prior to initiating any research activities.

Parental Power of Attorney:

A parent/legal caretaker will have the possibility of signing a power of attorney to the other parent/legal caretaker. Parents/legal caretakers will be informed that use of this form is voluntary and can be withdrawn at any time.

If only one parent has custody:
If one parent has sole custody, only this parent will give written informed consent to their child's participation in the research project. In this case, the research team will obtain necessary documentation for the parent's sole custody.

When the participant turns 18 years of age:
Participants who turn 18 years of age during the trial (within 2.5 years after inclusion) will receive new written and verbal information and be asked to give personal written informed consent in order to continue their study participation.

Parental participation:
Each parent/legal caretaker will receive their own written and verbal participant information and informed consent form regarding parental participation. If the parents do not give informed consent to be involved in the trial themselves, the adolescent patient with psychosis can still be included in the trial, if the above criteria for patient participation is fulfilled.

Participation of relevant clinicians and municipal collaborators:
At approx. 24 months (follow-up assessment) clinicians participating in the treatment in both the OPUS YOUNG intervention and in TAU will be invited to a semi-structured interview. Only a limited number will be invited from both treatments. Relevant municipal collaborators, taking part in the treatment and collaboration around the group of participants in the trial, will likewise be invited to participate in interviews.
Clinicians and municipal collaborators invited to participate in interviews, will receive written information brochures explaining the study background, procedures and aims, alongside the invitation. Consent will be obtained prior to participation in the interviews. The written information will inform about participants' rights to withdraw consent at any point.

Feasibility of the study

Based on data from the Danish Psychiatric Central Register and from the CAMHC local register, we expect to be able to recruit a minimum of 284 patients for the trial in the two-year period from June 1, 2021, to September 2023. This is realistic as we expect approximately 200 patients per year to be eligible for participating in the trial in the Capital Region in Denmark. The intervention part of the trial lasts for two years, but due to follow-up assessment six months after end of treatment, participation in the study is 2,5 years, i.e., the last randomized participant will conclude the intervention and trial end-point assessment September 31, 2025, and the 6-month follow-up assessment February 1, 2026 (see study plan, Table 2). The present study is a collaboration between the CAMHC and the adult mental health services (AMHS). Research in child and adolescent mental health is a prioritized focus area in the Mental Health Services of the Capital Region of Denmark, which supports and hosts the present study. Furthermore, the Danish Regions, covering all public health services in Denmark prioritizes in their 2020 recommendations for health research studies focusing on transition from child and adolescent health services to adult health services [128].

The CAMHC has ample experience in conducting clinical studies and trials on early onset psychosis [109,110] and the AMHS harbour the OPUS study [125,129,130], which has conducted trials and carried out a national implementation strategy of EIS in first-episode psychosis for 20 years. We expect patients and relatives to adhere to the two-years duration of OPUS YOUNG treatment as we have 20 years of positive experiences from the adult OPUS treatment, where the case manager's welcoming, assertive, competent, and cooperative approach have proven effectful for adherence. We expect this to be true for a younger age group as well, as the cooperation in CBCM is based on the same principles. Furthermore, as part of our preparations for the trial we have conducted a focus group interview with parents and patients who has been part of the piloting phase of the trial and who has received OPUS YOUNG treatment for periods of 1-6 months at the time of the interview. Both parents and patients expressed very positive evaluations of the OPUS YOUNG treatment, and provided helpful suggestions for adjustments of the program.

We acknowledge the efforts needed to recruit and maintain contact with everyone participating in the study. In CAMHS we have conducted several studies recruiting and including a total of more than 200 youths with first-onset psychosis below age 18 years. We are confident that we can engage patients in the OPUS YOUNG study, based on experience from managing the Tolerability and Efficacy of Antipsychotics (TEA) [109,131] trial, as well as our abilities to include patients with early-onset psychosis in clinical prospective neurobiological and cognitive studies [132–138].

Furthermore, we have vast experience from the OPUS I trial in which we succeed in an attrition of only 30% of all randomized patients at both 2, 5- and 10-years follow-up [125,129,139] as well as inclusion of 76,5% (90% in Aarhus and 63% in Copenhagen) of eligible patients [139].

Strengths and limitations

One of the main strengths of this trial is the use of a gold standard RCT design aiming to provide available evidence while minimizing bias. The use of a computer generated random sequence generation handled by an algorithm saved in REDCap [61] reduces the risk of selection bias. The use of blinded outcome assessors for outcomes and the use of intention-to-treat analysis aim to prevent biased effect estimates. All CAMHC patients in the catchment area who potentially meet inclusion criteria are offered to take part in the trial. Due to the very few exclusion criteria, the study will have high external validity.

The study builds on an evidence-based coordinated specialized assertive care model that has been proven efficient in young adults [125,129,140]. The study will provide novel results, since no previous studies have focused on EIS in patients below age 18 years. The current trial is supplemented with innovative and age-appropriate components aiming to target modifiable complications of early psychosis.

The fact that we are not able to blind the participants and staff might increase the risk of performance bias. The OPUS YOUNG treatment is a complex intervention, which makes it difficult to elucidate exactly which components are primarily responsible for the treatment effects. Due to the relatively few cases of psychosis in childhood and early adolescence, our sample will be small relative to adult samples. We have considered a multicentre trial but have weighted the strength of limiting the trial to one geography (short distance for group supervision and rating sessions, close cooperation with one clinic that provides a stable and uniform standard treatment).

Perspectives

A positive effect of specialized OPUS YOUNG treatment would be of great importance for future health-care planning to benefit young people with a first-episode psychosis. At the time being, we lack evidence to guide clinical practice for best treatment of this very severe mental disorder at a very important time of life. The present alternative is to extrapolate from EIS studies in adults, which cannot be considered evidenced based care, due to the specific needs of children and adolescents with psychosis. Youth have a right to access evidence-based treatment, which in this

case can only be addressed by conducting an RCT of EIS versus TAU. If this model proves to be more effective than TAU, it has an enormous potential for improving symptoms, function, recovery and adherence to treatment, adherence to school/education and thus to community and independent living, while at the same time reducing the need for hospitalization and society costs for this vulnerable patient group. Furthermore, we plan to assess follow-up at five years after end of trial.

Project organization and management

The trial will be carried out in the Capital Region of Denmark and will be co-ordinated by CAMHC and in collaboration with the adult mental health services (AMHS). Here, a series of interventional trials in different phases of schizophrenia spectrum disorders are already being conducted, ranging from high-risk and the early prodromal phase, and the early psychotic phase to later phases with specialized interventions for co-morbid substance abuse and neurocognitive deficits.

The steering committee consists of researchers with massive expertise on early and first-onset psychosis and with profound trial experience. Importantly, experienced clinicians are represented in the steering committee to ensure a close collaboration between research and clinic throughout the process. The study group has extensive international networks on EIS and the treatment of psychosis in childhood and adolescence, and the advisory board for the present study will include experts on these areas and on transition and complex interventions.

Principal investigator: Anne Katrine Pagsberg, professor, MD, PhD, senior consultant (child and adolescent psychiatry) and senior researcher, CAMHC.

Co-investigator (until December 2021): Marianne Melau, MSc, PhD, senior researcher CAMHC.

Steering committee: Anne Katrine Pagsberg, professor, MD, PhD, senior consultant (child and adolescent psychiatry) and senior researcher, CAMHC, area of expertise; PI for pharmacological and non-pharmacological clinical interventions; Marianne Melau, MSc, PhD, senior researcher CAMHC; area of expertise: Early intervention in psychosis (investigator in OPUS), CBCM, MFG, program fidelity; Merete Nordentoft, professor, MD, MSc, PhD, senior consultant (Psychiatry) AMHS, area of expertise: PI for several large RCT incl. OPUS; Pia Jeppesen, associate professor, MD, PhD, senior consultant (child and adolescent psychiatry) and senior researcher (CAMHC) area of expertise; PI of RCT (Mind My Mind trial) and investigator in OPUS, MFG experience. Anne Amalie Elgaard Thorup, professor, MD, PhD, senior consultant (child and adolescent psychiatry) and senior researcher (CAMHC) area of expertise: RCT in high risk for psychosis, and investigator in OPUS; Jens Richardt Jepsen, psychologist, PhD, senior researcher, (AMHS and CAMHS), area

of expertise: neurocognition, early onset psychosis; Lene Halling Hastrup, Senior Researcher, Health Economist, PhD, Psychiatric Research Unit, Psychiatry Region Zealand, area of expertise: health economy. The centre management and clinicians will be represented by Elisabeth Bille Brahe, clinical quality manager (CAMHS); Lis Raabæk Olsen, senior consultant (CAMHS), MD, PhD; Jacob Rydkjær senior consultant, MD, PhD (CAMHS).

*Advisory board***:** Professor Max Birchwood, MSc psychology, Mental Health and Wellbeing, University of Warwick, Coventry, United Kingdoms; Professor of Youth Mental Health Patrick McGorry MD PhD, Executive Director, University of Melbourne; Professor of Child and adolescent psychiatry, Psychiatry and Molecular Medicine Christoph Correll, Professor of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany and The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Hempstead, NY, USA; Professor Swaran P Singh, Head, Mental Health and Wellbeing Deputy Head, Division of Health Sciences Warwick Medical School, University of Warwick. Ditte Lammers Vernal, MSc psychology, PhD, Aalborg University Hospital, Denmark.

Management of the project (co-ordinating investigator). The Ph.D.-students involved in the project will benefit from being involved with researchers who have worked with clinical and epidemiological research in schizophrenia spectrum disorders for many years and from the excellent opportunities for international collaboration. All assessments will be carried out by researchers and Ph.D.-students, trained in all instruments used in the study before study start.

Sharing of depersonalized data

We will share the depersonalized data at www.clinicaltrials.gov.

Publications and dissemination policy

The OPUS YOUNG treatment approach will be manualized. Comprising a manual for CBCM, SCIT and MFG as it is delivered in OPUS YOUNG. Furthermore, and inspired by The Raise program for Coordinated Specialty Care for First Episode Psychosis in USA [87], we will offer the OPUS YOUNG manual online designed to guide implementation of future OPUS YOUNG team together with education programs that cover core elements in OPUS YOUNG treatment.

Results from the analysis of data in OPUS YOUNG will be published in peer-reviewed international scientific journals.

PhD projects

The OY trial has planned five PhD studies (A-E):

A. The characteristics of the study population and pathways to care, the use of health care, and social services prior to study inclusion based on baseline data from all included participants and data from the Danish National Registers. (2021-2023)

B. Benefits and harms of OY vs. TAU: Analysis of the primary and secondary/exploratory outcomes of the RCT and testing the two main hypotheses, 1) that OY is more effective than TAU in improving social functioning, and 2) that OY will be more effective than TAU in reducing positive and negative psychosis symptoms and provide a higher client satisfaction and health related quality of life. Furthermore, the PhD will analyze self-efficacy, experience of service, treatment alliance and adherence, the use of pharmacotherapy, school adherence, family burden, siblings' perceived stress, substance misuse, and adverse treatment effects. This PhD will also analyze the sustained effects at 6 months follow-up for OY vs. TAU. (2023-2026)

C. User perspectives on trans-sectorial activities in OY vs. TAU: The primary focus in this PhD is to investigate and describe the trans-sectorial activities (the collaborations of OY/TAU with municipal and school services) and analyze whether the amount and quality of trans-sectorial activities is an effect moderator for outcomes at 24 months (end of trial) and 30 months (follow-up). Drawing on semi-structured interviews at approx. 24 months (end of trial, follow-up), clinical, and register data the study includes perspectives from patients, parents/legal caretakers, clinicians, and municipal collaborators on trans-sectorial activities and the quality of the collaboration.(2024-2026)

D. Clinical and cognitive Illness trajectories in OY vs TAU: To explore the detailed symptomatic and diagnostic illness trajectories as well as the cognitive and social cognitive trajectories during the first two years of early onset psychosis. Cluster analysis will be used to determine psychosis subgroups based on symptom/cognitive deficits heterogeneity and their course. Growth mixture

modeling (GMM) analysis will be used to identify distinct treatment response patterns for OY vs. TAU. The results will substantiate efforts to individualize future treatments based on patient subgroup profiles. Predictors of treatment effects will be evaluated using all available information from the examinations during the trial and the Danish National Registers. (2024-2026)

E. Cost-effectiveness of OY vs. TAU: To investigate the cost-effectiveness of OY vs. TAU, in to inform decision makers concerning the cost and benefits of the OY intervention. Cost-utility analyses (CUA) will be carried out for the trial period. The CUAs will be conducted from an extended health sector perspective and include the costs of all interventions directed toward the individual youth's mental health problems no matter the provider of services. Uncertainty about the long-term effects limits the possibilities of carrying out formal decision analytic modelling but can be handled by analyzing different possible scenarios in extrapolation scenarios of the development in health-related quality of life (HRQoL). Costs (of OY and TAU) will be estimated at the individual participant level. Youths are assessed for HRQoL using the Child Health Utility 9-Dimension (CHU-9D) and EQ-5D. CHU-9D is a generic preference-based HRQoL-measure constructed for use in children and youth while EQ-5D is a generic preference-based HRQoL-measure constructed for use in youth and adults. We will measure the value of health outcomes in Quality-Adjusted Life Years (QALY). Health states will be defined using CHU-9D and EQ-5D. We will analyze the Incremental Cost-Effectiveness Ratio (ICER). (2024-2026)

The PhD studies will benefit from the international collaboration with highly experienced researchers with expertise in clinical and epidemiological research in schizophrenia spectrum disorders.
We will communicate all trial results, both positive, negative as well in-conclusive results, to health-care professionals, service users, policy makers and other relevant groups.

Reference List

1 Eggers C. Course and prognosis of childhood schizophrenia. *J Autism Child Schizophr* 1978;**8**:21–36.

2 Remschmidt H, Theisen FM. Schizophrenia and related disorders in children and adolescents. *J Neural Transm Suppl* Published Online First: 2005. doi:10.1007/3-211-31222-6_7

3 Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, *et al.* Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. *J Child Adolesc Psychopharmacol* 2016;**26**:410–27. doi:10.1089/cap.2015.0097

4 Schimmelmann BG, Schmidt SJ, Carbon M, *et al.* Treatment of adolescents with early-onset schizophrenia spectrum disorders: In search of a rational, evidence-informed approach. Curr. Opin. Psychiatry. 2013. doi:10.1097/YCO.0b013e32835dcc2a

5 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* Published Online First: 2014. doi:10.1111/eip.12007

6 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. 2018. doi:10.1001/jamapsychiatry.2018.0623

7 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. Published Online First: 2016. doi:10.1176/appi.ajp.2015.15050632

8 Kuhl JO, Laursen TM, Thorup A, *et al.* The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000-2012. A register-based study. *SchizophrRes* 2016;**176**:533–9.

9 Dalsgaard S, Thorsteinsson E, Trabjerg BB, *et al.* Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA Psychiatry* 2020;**77**:155–64. doi:10.1001/jamapsychiatry.2019.3523

10 Kahn Rene I, Sommer IE, Murray RM, Meyer-lindenberg A, *et al.* Schizophrenia. *Nat Rev Dis Prim* 2015;**1**. doi:10.1038/nrdp.2015.67

11 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* 2012;**380**:2129–43. doi:10.1016/S0140-6736(12)61680-8

12 Jääskeläinen E, Juola P, Hirvonen N, *et al.* A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull* 2013;**39**:1296–306. doi:10.1093/schbul/sbs130

13 Jennifer P. Wisdom, Jennifer I. Manuel, and Robert E. Drake. Substance Use Disorder Among People With First-Episode Psychosis: A Systematic Review of Course and Treatment. *Psychiatr Serv Publ online first* 2011;**62**:1007–12. doi:10.1176/appi.ps.62.9.1007.Substance

14 Maniglio R. Review article Severe mental illness and criminal victimization : a systematic review. *Acta PsychiatrScand* 2009;**119**:180–91. doi:10.1111/j.1600-0447.2008.01300.x

15 Munkner R, D M, Haastrup S, *et al.* Incipient offending among schizophrenia patients after first contact to the psychiatric hospital system. *EurPsychiatry Publ online first* 2005;**20**:321–6. doi:10.1016/j.eurpsy.2005.01.008

16 Fazel S, Gulati G, Linsell L, *et al.* Schizophrenia and Violence : Systematic Review and. *PLoSOne* 2009;**6**. doi:10.1371/journal.pmed.1000120

17 Dalsgaard S, McGrath J, Østergaard SD, *et al.* Association of mental disorder in childhood

and adolescence with subsequent educational achievement. *JAMA Psychiatry* 2020;**77**:797–805. doi:10.1001/jamapsychiatry.2020.0217
18 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**:A42.
19 Nordentoft M, Wahlbeck K, Hallgren J, *et al.* Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. PLoS.One. 2013;**8**:e55176-.
20 Hjorthøj C, Stürup AE, McGrath JJ, *et al.* Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *The lancet Psychiatry* 2017;**4**:295–301. doi:10.1016/S2215-0366(17)30078-0
21 Nielsen RE, Uggerby AS, Jensen SOW, *et al.* 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**:22–7. doi:10.1016/j.schres.2013.02.025
22 Ph D, Reed T, Compton MT, *et al.* Demographic, socio-environmental, and substancerelated predictors of duration of untreated psychosis (DUP). *SchizophrRes* 2013;**148**:93–8. doi:10.1016/j.schres.2013.05.011.Demographic
23 Chan SW. Global Perspective of Burden of Family Caregivers for Persons With Schizophrenia. *Arch Psychiatr Nurs* 2011;**25**:339–49. doi:10.1016/j.apnu.2011.03.008
24 Cuijpers P SH. Burnout Among Relatives of Psychiatric Patients Attending Psychoeducational Support Groups. *Psychiatr Serv* 2000;**51**.
25 Martens J AJ. The psychological well-being of family members of individuals with schizophrenia. *SocPsychiatry PsychiatrEpidemiol* 2001;**36**:128–33.
26 Jin H MI. The Societal Cost of Schizophrenia: A Systematic Review. Pharmacoeconomics. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc13&NEWS=N&AN=2016-09026-001. 2016.
27 McDaid D, Park A, Iemmi V, *et al.* Growth in the use of early intervention for psychosis services: An opportunity to promote recovery amid concerns on health care sustainability. *London Sch Econ* 2016.
28 Nordentoft M, Rasmussen JØ, Melau M, *et al.* How successful are first episode programs ? A review of the evidence for specialized assertive early intervention. *Curr Opin Psychiatry* 2020;**27**:167–72. doi:10.1097/YCO.0000000000000052
29 McDaid D, Park A-L, Iemmi V et al. Growth in the use of early intervention for psychosis services: an opportunity to promote recovery amid concerns on health care sustainability. http//eprints.lse.ac.uk/65630/1/__lse.ac.uk_storage_LIBRARY_Secondary_libfile_shared_repository_Content_PSSRU_Growth use early Interv. 2016.
30 Hastrup LH, Kronborg C, Bertelsen M, *et al.* Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). Br.J.Psychiatry. ;**202**:35–41.
31 Singh SP, Anderson B, Liabo K, *et al.* Supporting young people in their transition to adults' services: summary of NICE guidance. *BMJ* 2016;**353**:i2225. doi:10.1136/bmj.i2225
32 Bpf R, Hammels C, Geschwind N. Resilience in mental health : linking psychological and neurobiological perspectives. 2013;:3–20. doi:10.1111/acps.12095
33 GCP Quideline. 2017.https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf
34 *World Health Organisation. ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidlines*. Geneva: : World Health Organisation 1992.
35 Hsfner H, Hambrecht M, Maurer K, *et al.* IRAOS : an instrument for the assessment of onset and early course of schizophrenia. *SchizophrRes* 1992;**6**:209–23.

36 Kaufman J, Birmaher B, Brent D, *et al.* Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:980–8.
37 Andreasen NC. *The scale for the assessment of positive symptoms (SAPS)*. Iowa: : The University of Iowa 1984. doi:10.4236/oalib.1100693
38 Andreasen NC. *The scale for the assessment of negative symptoms (SANS)*. Iowa City: : The University of Iowa 1984.
39 HAMILTON M, M.A. H. A rating scale for depression. *J Neural Neurosurg Psychiatry* 1960;**23**:56–62.
40 Timmerby N, Andersen JH, Søndergaard S, *et al.* A Systematic Review of the Clinimetric Properties of the 6-Item Version of the Hamilton Depression Rating Scale (HAM-D6). *Psychother Psychosom* Published Online First: 2017. doi:10.1159/000457131
41 Guy W. *ECDEU Assessment Manual for Psychopharmacology: Revised.* 1976.
42 Guy W. *Clinical and Global Impressions. ECDEU Assessment Manual for Psychopharmacology. Reviced*. Rockville: : National Institute of Mental Health 1976.
43 Morosini PL, Magliano L, Brambilla L, Ugolini S PR. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;**101**:323–9.
44 Wechsler D. Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). *San Antonio* 2008.
45 Keefe RS, Goldberg TE, Harvey PD, *et al.* The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr.Res. ;**68**:283–97.
46 Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: Investigating "theory of mind" in people with schizophrenia. *Schizophr Res* 1995;**17**:5–13. doi:10.1016/0920-9964(95)00024-G
47 Dam VH, Thystrup CK, Jensen PS, *et al.* Psychometric Properties and Validation of the EMOTICOM Test Battery in a Healthy Danish Population. *Front Psychol* 2019;**10**. doi:10.3389/fpsyg.2019.02660
48 Bland AR, Roiser JP, Mehta MA, *et al.* EMOTICOM: A neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition. *Front Behav Neurosci* 2016;**10**. doi:10.3389/fnbeh.2016.00025
49 Ravens-Sieberer U, Erhart M, Rajmil L, *et al.* Reliability, construct and criterion validity of the KIDSCREEN-10 score: A short measure for children and adolescents' well-being and health-related quality of life. *Qual Life Res* Published Online First: 2010. doi:10.1007/s11136-010-9706-5
50 Stevens K. Developing a descriptive system for a new preference-based measure of health-related quality of life for children. *Qual Life Res* 2009;**18**:1105–13. doi:10.1007/s11136-009-9524-9
51 Group E. EuroQol: a new facility for the measurement of health related quality of life. *Health Policy (New York)* 1990;**16**:199–208.
52 Luszczynska A, Scholz U, Schwarzer R. The general self-efficacy scale: multicultural validation studies. J.Psychol. ;**139**:439–57.
53 Horvath AO, Greenberg LS. Development and Validation of the Working Alliance Inventory. *J Couns Psychol* Published Online First: 1989. doi:10.1037/0022-0167.36.2.223
54 Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Eval.Program.Plann.

1982;**5**:233–7.
55 Rozental A, Kottorp A, Boettcher J, *et al.* Negative Effects of Psychological Treatments : An Exploratory Factor Analysis of the Negative Effects Questionnaire for Monitoring and Reporting Adverse and Unwanted Events. 2016;:1–22. doi:10.1371/journal.pone.0157503
56 TEM. https://psy.au.dk/fileadmin/site_files/filer_rusmiddelforskning/dokumenter/redskaber/TEM_standard.pdf
57 Nielsen T, Pontoppidan M, Rayce SB. The Parental Stress Scale revisited: Rasch-based construct validity for Danish parents of children 2–18 years old with and without behavioral problems. *Health Qual Life Outcomes* 2020;**18**:281. doi:10.1186/s12955-020-01495-w
58 Epstin N., Baldwin L. BD. McMaster Family Assessment Device. 1983.
59 Ahlfors UG, Bech P, Dencker SJ, *et al.* The UKU side effect rating scale Psychiatrica. *Acta Psychiatr Scand* 1987;**76**.
60 Dodzik P. Behavior Rating Inventory of Executive Function, Second Edition Gerard A. Gioia, Peter K. Isquith, Steven C. Guy, and Lauren Kenworthy. *J Pediatr Neuropsychol* 2017;**3**:227–31. doi:10.1007/s40817-017-0044-1
61 Harris PA, Taylor R, Thielke R, *et al.* Research Electronic Data Capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. doi:10.1016/j.jbi.2008.08.010
62 Hartmann JA, Mcgorry D, Schmidt J, *et al.* Opening the Black Box of Cognitive-Behavioural Case Management in Clients with Ultra-High Risk. 2017;**3052**:292–9. doi:10.1159/000477551
63 Godolphin W. Shared decision-making. *HealthcQ* 2009;**12 Spec No**:e186–90.
64 Stein LI, A.B. S. Assertive Community Treatment of persons with evere mental illness. 1998.
65 McFarlane WR, Lukens E, Link B, *et al.* Multiple-family groups and psychoeducation in the treatment of schizophrenia. Arch.Gen.Psychiatry. 1995;**52**:679–87.
66 Sin J, Cd J, Ea B, *et al.* Psychoeducation for siblings of people with severe mental illness (Review). *CochraneDatabaseSystRev* Published Online First: 2015. doi:10.1002/14651858.CD010540.pub2.www.cochranelibrary.com
67 Bowman S, Alvarez-jimenez M, Wade D, *et al.* The Positive and Negative Experiences of Caregiving for Siblings of Young People with First Episode Psychosis. 2017;**8**:1–14. doi:10.3389/fpsyg.2017.00730
68 Penn DL, Roberts DL, Combs D, *et al.* Best Practices: The Development of the Social Cognition and Interaction Training Program for Schizophrenia Spectrum Disorders. *Psychiatr Serv* 2007;**58**:449–51. doi:10.1176/appi.ps.58.4.449
69 Roberts DL, Penn DL, Labate D, *et al.* Transportability and feasibility of Social Cognition and Interaction Training (SCIT) in community settings. *Behav Cogn Psychother* Published Online First: 2010. doi:10.1017/S1352465809990464
70 Nelson B, Amminger GP, Yuen HP, *et al.* NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders-medium-term follow-up and clinical course. *NPJSchizophr* 2018;**4**:11. doi:10.1038/s41537-018-0052-x
71 Robinson DG, Schooler NR, Ph D, *et al.* Psychopharmacological Treatment in the RAISE-ETP Study : Outcomes of a Manual and Computer Decision Support System Based Intervention. *AmJPsychiatry* 2018;:169–79. doi:10.1176/appi.ajp.2017.16080919
72 Behandlingsvejledninger. Antipsykotika-til-born-og-unge. https://medicinraadet.dk/anbefalinger-og-vejledninger/behandlingsvejledninger/antipsykotika-til-born-og-unge

73 Nelson B, Amminger GP, Yuen HP, *et al.* NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders-medium-term follow-up and clinical course. *NPJSchizophr* 2018;**4**:11.
74 Mueser KT, Penn DL, Addington J, *et al.* The NAVIGATE Program for First-Episode Psychosis: Rationale, Overview, and Description of Psychosocial Components. *Psychiatr Serv* Published Online First: 2015. doi:10.1176/appi.ps.201400413
75 Horvath A, Symonds B. Relation between working alliance and outcome in psychoterapy: A meta-analysis. J. Couns. Psychol. 1991;**28**:139–49.
76 Melau M, Harder S, Jeppesen P, *et al.* The association between working alliance and clinical and functional outcome in a cohort of 400 patients with first-episode psychosis: A cross-sectional study. *J Clin Psychiatry* 2015;**76**:e83–90. doi:10.4088/JCP.13m08814
77 McFarlane WR, Dixon L, Lukens E, *et al.* Family psychoeducation and schizophrenia: a review of the literature. J.Marital Fam.Ther. 2003;**29**:223–45.
78 Pilling S, Bebbington P, Kuipers E, *et al.* Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychol Med* 2002;**32**:783–91.
79 Pitschel-Walz G, Leucht S, Bäuml J, *et al.* The effect of family interventions on relapse and rehospitalization in schizophrenia--a meta-analysis. *Schizophr Bull* 2001;**27**:73–92.
80 Lucksted A, McFarlane W, Downing D, *et al.* Recent developments in family psychoeducation as an evidence-based practice. *JMarital FamTher* 2012;**38**:101–21.
81 Fjell A, Bloch Thorsen GR, Friis S, *et al.* Multifamily group treatment in a program for patients with first-episode psychosis: experiences from the TIPS project. *Psychiatr Serv* 2007;**58**:171–3. doi:10.1176/ps.2007.58.2.171
82 Sin J, Moone N, Harris P, *et al.* Original Article Understanding the experiences and service needs of siblings of individuals with first-episode psychosis : a phenomenological study. *Early IntervPsychiatry* 2012;:53–9. doi:10.1111/j.1751-7893.2011.00300.x
83 Friedrich Rose Marie, Lively Sonja RLM. Siblings ' Coping Strategies and Mental Health Services : A National Study of Siblings of Persons With Schizophrenia. *Psychiatr Serv* 2008;**59**:261–7.
84 Amt P i Aa. No Title. Søskende til Psyk. syge. 2005;:https://www.google.dk/amp/s/docplayer.dk/amp/11074.
85 Boyer L, Millier A, Perthame E, *et al.* Quality of life is predictive of relapse in schizophrenia. *BMC Psychiatry* 2013;**13**:15. doi:10.1186/1471-244X-13-15
86 Caqueo-Urízar A, Boyer L, Baumstarck K, *et al.* Subjective perceptions of cognitive deficits and their influences on quality of life among patients with schizophrenia. *Qual Life Res* 2015;**24**:2753–60. doi:10.1007/s11136-015-1019-2
87 Green MF, Kern RS, Braff DL, *et al.* Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* 2000;**26**:119–36.
88 Wykes T, Spaulding WD. Thinking About the Future Cognitive Remediation Therapy--What Works and Could We Do Better? *Schizophr Bull* 2011;**37**:S80–90. doi:10.1093/schbul/sbr064
89 Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;**153**:321–30. doi:10.1176/ajp.153.3.321
90 L B. The social brain: a project for integrating primate behavior and neurophysiology in new domain. *Concept Neurosci* 1990;**1**:27–61.
91 Bartholomeusz CF, Allott K, Killackey E, *et al.* Social cognition training as an intervention for improving functional outcome in first-episode psychosis: A feasibility study. *Early Interv*

Psychiatry Published Online First: 2013. doi:10.1111/eip.12036
92 Combs DR, Adams SD, Penn DL, *et al.* Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: preliminary findings. *SchizophrRes* 2007;**91**:112–6.
93 Kuipers E, Yesufu-Udechuku A, Taylor C, *et al.* Management of psychosis and schizophrenia in adults: Summary of updated NICE guidance. BMJ. 2014. doi:10.1136/bmj.g1173
94 Jauhar S, McKenna PJ, Radua J, *et al.* Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. Br. J. Psychiatry. 2014. doi:10.1192/bjp.bp.112.116285
95 Laws KR, Darlington N, Kondel TK, *et al.* Cognitive Behavioural Therapy for schizophrenia-outcomes for functioning, distress and quality of life: a meta-analysis. *BMC Psychol* Published Online First: 2018. doi:10.1186/s40359-018-0243-2
96 Anagnostopoulou N, Kyriakopoulos M, Alba A. Psychological interventions in psychosis in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry* Published Online First: 2018. doi:https://dx.doi.org/10.1007/s00787-018-1159-3
97 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* Published Online First: 2016. doi:10.1176/appi.ajp.2015.15050632
98 Kendall T, Hollis C, Stafford M, *et al.* Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance. *BMJ* 2013;**346**:f150. doi:10.1136/bmj.f150
99 Ray WA, Stein CM, Murray KT, *et al.* Association of Antipsychotic Treatment With Risk of Unexpected Death Among Children and Youths. *JAMA Psychiatry* 2019;**37212**:162–71. doi:10.1001/jamapsychiatry.2018.3421
100 Krause M, Zhu Y, Huhn M, *et al.* Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *Eur Neuropsychopharmacol* 2018;**28**:659–74. doi:10.1016/j.euroneuro.2018.03.008
101 Pagsberg AK, Tarp S, Glintborg D, *et al.* Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. *J Am Acad Child Adolesc Psychiatry* 2017;**56**:191–202. doi:10.1016/j.jaac.2016.12.013
102 Killackey E, Jackson HJ, McGorry PD. Vocational intervention in first-episode psychosis: individual placement and support v. treatment as usual. *BrJPsychiatry* 2008;**193**:114–20.
103 NICE: Psychosis and schizophrenia in children and young people: recognition and management. 2016.https://www.nice.org.uk/guidance/cg155/chapter/Recommendations#promoting-recovery-and-providing-possible-future-care-in-secondary-care
104 Gates PJ, Sabioni P, Copeland J, *et al.* Psychosocial interventions for cannabis use disorder. *Cochrane Database Syst Rev* Published Online First: 5 May 2016. doi:10.1002/14651858.CD005336.pub4
105 Pedersen M.U. & Pedersen M.M. MOVE. 21 måneder efter indskrivning. Aarhus, Denmark: 2019.
106 Pedersen M.U., Pedersen M.M., Jones S., Skov K.B.E. FK t. Behandling af unge, der misbruger stoffer. En undersøgelse af 4 behandlingsmetoders effek. Aarhus, Denmark: 1917.
107 Pedersen MU, Jones S, Skov KBE, Frederiksen KS PM. *MOVE. Struktureret, forstærkende rusmiddelbehandling: Manual.* AArhus Denmark: : Center for Rusmiddelforskning, Aarhus

Universitet 2019.
108 NICE: Coexisting servere mental illness and substance misuse: assessment amd management in healthcare settings overview. 2018.https://www.nice.org.uk/guidance/ng58
109 Jensen KG, Gärtner S, Correll CU, *et al.* Change and dispersion of QT interval during treatment with quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: results from the TEA trial. *Psychopharmacology (Berl)* 2018;**235**:681–93. doi:10.1007/s00213-017-4784-5
110 Jensen KG, Correll CU, Rudå D, *et al.* Pretreatment Cardiometabolic Status in Youth With Early-Onset Psychosis. *J Clin Psychiatry* 2017;**78**:e1035–46. doi:10.4088/JCP.15m10479
111 Leggatt M, Woodhead G. Early Intervention in the Real World Family peer support work in an early intervention youth mental health service. *Early IntervPsychiatry* 2016;:1–6. doi:10.1111/eip.12257
112 Sundhedsstyrelsen. Sundhedsstyrelsen. Specialevejledning for Børne- og ungdomspsykiatri. 2019.https://www.sst.dk/-/media/Viden/Specialplaner/Specialeplan-for-børne--og-ungdomspsykiatri/SST_Specialevejledning-for-boeerne-og-ungdomspsykiatri-11-april-2019.ashx?la=da&hash=BCF7C83B6D6DB5291B621A6805C841CADD2EA137
113 Nielsen CM, Hjorthøj C, Killaspy H, *et al.* The effect of flexible assertive community treatment in Denmark: a quasi-experimental controlled study. *The Lancet Psychiatry* 2021;**8**:27–35. doi:10.1016/S2215-0366(20)30424-7
114 Broersen M, Frieswijk N, Kroon H, *et al.* Young Patients With Persistent and Complex Care Needs Require an Integrated Care Approach: Baseline Findings From the Multicenter Youth Flexible ACT Study. *Front Psychiatry* Published Online First: 2020. doi:10.3389/fpsyt.2020.609120
115 Addington D, Birchwood M, Jones P, *et al.* Fidelity scales and performance measures to support implementation and quality assurance for first episode psychosis services. *Early IntervPsychiatry* 2018.
116 Melau M, Albert N, Nordentoft M. Development of a fidelity scale for Danish specialized early interventions service. *Early Interv Psychiatry* Published Online First: 28 November 2017. doi:10.1111/eip.12523
117 Melau M, Albert N, Nordentoft M. Programme fidelity of specialized early intervention in Denmark. *Early Interv Psychiatry* 2018;:1–6. doi:10.1111/eip.12549
118 Ulloa R-E, Apiquian R, Victoria G, *et al.* Validity and reliability of the Spanish version of the Personal and Social Performance scale in adolescents with schizophrenia. *Schizophr Res* 2015;**164**:176–80. doi:10.1016/j.schres.2015.02.010
119 Petrić D, Rački V, Gačo N, *et al.* Retrospective Analysis of the Effectiveness and Tolerability of Long-Acting Paliperidone Palmitate Antipsychotic in Adolescent First-Episode Schizophrenia Patients. *J Child Adolesc Psychopharmacol* 2019;**29**:197–204. doi:10.1089/cap.2018.0044
120 Pérez-Garza R, Victoria-Figueroa G, Ulloa-Flores RE. Sex Differences in Severity, Social Functioning, Adherence to Treatment, and Cognition of Adolescents with Schizophrenia. *Schizophr Res Treatment* 2016;**2016**:1–7. doi:10.1155/2016/1928747
121 Albert N, Melau M, Jensen H, *et al.* Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II). *BMJ* 2017;**356**:i6681. doi:10.1136/bmj.i6681
122 Petersen L, Jeppesen P, Thorup A, *et al.* treatment for patients with a first episode of psychotic illness. *BMJ* 2005;**01**:1–7. doi:10.1136/bmj.38565.415000.E01
123 Pagsberg AK, Jeppesen P, Klauber DG, *et al.* Quetiapine extended release versus

aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *The Lancet Psychiatry* 2017;**4**:605–18. doi:10.1016/S2215-0366(17)30166-9
124 Jakobsen JC, Gluud C, Wetterslev J, *et al.* When and how should multiple imputation be used for handling missing data in randomised clinical trials - A practical guide with flowcharts. *BMC Med Res Methodol* 2017;**17**. doi:10.1186/s12874-017-0442-1
125 Petersen L, Jeppesen P, Thorup A, *et al.* A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ* 2005;**331**:602-. doi:10.1136/bmj.38565.415000.E01
126 Ravens-Sieberer U, Erhart M, Rajmil L, *et al.* Reliability, construct and criterion validity of the KIDSCREEN-10 score: a short measure for children and adolescents' well-being and health-related quality of life. *Qual Life Res* 2010;**19**:1487–500. doi:10.1007/s11136-010-9706-5
127 Glick HA, Doshi JA, Sonnad SS D. *Polsky Economic evaluation in clinical trials*. New York, United States: 2007.
128 Danske Regioner. Forskning – vejen til god og effektiv diagnostik og behandling af psykisk sygdom. 2020.https://www.regioner.dk/media/13721/mental-sundhed-mere-forskning-om-god-diagnostik-og-behandling-af-psykisk-sygdom.pdf
129 Bertelsen M, Jeppesen P, Petersen L, *et al.* 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. Arch.Gen.Psychiatry. ;**65**:762–71.
130 Albert N, Melau M, Jensen H, *et al.* Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II). *BMJ* 2017;**356**:i6681.
131 AK P, Jeppesen P, DG K, *et al.* _Quetiapine extended release versus aripiprazole in children and adolescents with first episode psychosis: the double-blind randomised Tolerability and Efficacy of Antipsychotics (TEA) trial._. Lancet Psychiatry. 2017.
132 Pagsberg AK, Fagerlund B, Oranje B, *et al.* Mismatch negativity and P3a amplitude in young adolescents with fi rst-episode psychosis : a comparison with ADHD. *PsycholMed* 2017;**47**:377–88. doi:10.1017/S0033291716002518
133 Jepsen JRMM, Rydkjaer J, Fagerlund B, *et al.* Overlapping and disease specific trait, response, and reflection impulsivity in adolescents with first-episode schizophrenia spectrum disorders or attention-deficit/hyperactivity disorder.No Title. *PsycholMed* 2018;**48**:604–16. doi:10.1017/S0033291717001921
134 Jepsen JRM, Fagerlund B, Pagsberg AK, *et al.* Profile of cognitive deficits and associations with depressive symptoms and intelligence in chronic early-onset schizophrenia patients. *ScandJPsychol* 2013;**54**:363–70. doi:10.1111/sjop.12062
135 Richardt J, Birgitte MJ, Katrine A, *et al.* Deficient maturation of aspects of attention and executive functions in early onset schizophrenia. *EurChild AdolescPsychiatry* 2010;**19**:773–86. doi:10.1007/s00787-010-0126-4
136 Jepsen JRM, Fagerlund B, Pagsberg AK, *et al.* Course of intelligence deficits in early onset , first episode schizophrenia : a controlled , 5-year longitudinal study. *EurChild AdolescPsychiatry* 2010;**19**:341–51. doi:10.1007/s00787-009-0053-4
137 Christensen AMR, Fagerlund B, Hansen M-BB, *et al.* Structural brain abnormalities in early onset first-episode psychosis. *J Neural Transm* 2007;**114**:489–98. doi:10.1007/s00702-006-0573-8
138 Fagerlund B, Pagsberg AK, Hemmingsen RP. Cognitive deficits and levels of IQ in

adolescent onset schizophrenia and other psychotic disorders. *SchizophrRes* 2006;**85**:30–9. doi:10.1016/j.schres.2006.03.004
139 Secher RG, Hjorthoj CR, Austin SF, *et al.* Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. Schizophr.Bull. ;**41**:617–26.
140 Albert N, Melau M, Jensen H, *et al.* Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II). *BMJ* 2017;**356**:i6681.