The FOCUS trial: cognitive remediation plus standard treatment versus standard treatment for patients at ultra-high risk for psychosis: study protocol for a randomised controlled trial

Louise B Glenthøj1,2*, Birgitte Fagerlund2,3, Lasse Randers1,2, Carsten R Hjorthøj1, Christina Wenneberg1,2, Kristine Krakauer1,2, Astrid Vosgerau1,4, Christian Gluud5, Alice Medalia6, David L Roberts7 and Merete Nordentoft1,2

Abstract

Background: Cognitive deficits are a distinct feature among people at ultra-high risk (UHR) for psychosis and pose a barrier to functional recovery. Insufficient evidence exists on how to ameliorate these cognitive deficits in patients at UHR for psychosis and hence improve daily living and quality of life. The aim of the trial is to investigate whether cognitive remediation can improve cognitive and psychosocial function in patients at UHR for psychosis.

Methods: The FOCUS trial (Function and Overall Cognition in Ultra-high risk States) is a randomised, parallel group, observer-blinded clinical trial enrolling 126 patients meeting the standardised criteria of being at UHR for psychosis. Patients are recruited from psychiatric in- and outpatient facilities in the Copenhagen catchment area. Patients are randomised to one of the two treatment arms: cognitive remediation plus standard treatment versus standard treatment. The cognitive remediation consists of 24 weekly group-based and manualised sessions targeting neurocognition and social cognition. In addition to the group sessions, the patients will be offered 12 individual sessions aiming at maximising the transfer of the effects of the cognitive training to their everyday lives. Follow-up assessments will be conducted at 6 and 12 months after randomisation. The primary outcome is the composite score on the Brief Assessment of Cognition in Schizophrenia at cessation of treatment after 6 months. Secondary outcomes are social and daily functioning, psychosis-like symptoms, negative symptomatology, and depressive symptomatology as measured with the Personal and Social Performance Scale, Brief Psychiatric Rating Scale-Expanded Version, Scale for the Assessment of Negative Symptoms, and the Montgomery-Åsberg Depression Rating Scale.

Discussion: This is the first trial to evaluate the effects of neurocognitive and social cognitive remediation in UHR patients. The FOCUS trial results will provide evidence on the effect of targeted and comprehensive cognitive rehabilitation on cognition, daily living, and symptomatology as well as long-term outcome in preventing transition to psychosis in UHR patients.

Trial registration: ClinicalTrials.gov NCT 02098408. Date of registration 18 March 2014.

Keywords: At-risk mental state, Ultra-high risk for psychosis, Prodromal schizophrenia, Prodromal intervention, Cognitive remediation, Cognitive training, Social cognitive training, Neurocognitive training
Background

The prodromal phase of schizophrenia and other psychotic disorders

Schizophrenia is a debilitating disorder with a point prevalence of 0.6% [1]. The construct of the ultra-high-risk (UHR) state for schizophrenia and other psychotic disorders captures the putative prodromal phase of psychosis, which is seen as a forerunner of frank psychosis. Patients in this UHR state present discrete yet identifiable psychotic symptoms. Intervention studies targeting the UHR state for psychosis have increased during the last decade [2]. Potentially, such interventions could avoid, ameliorate, or delay progression to psychosis. Furthermore, initiating appropriate treatment as early as possible has the potential to improve both the clinical and functional outcomes of patients.

The most recent meta-analysis on prodromal intervention in psychosis assessed 10 randomised clinical trials aiming at preventing psychosis [3]. The intervention strategies in these trials encompass antipsychotic medication, omega-3 fatty acids, psychosocial, and cognitive behavioural interventions and integrative therapy [4-13]. The results from these trials are promising, but evidence is still too scarce to be conclusive. None of the studies on prodromal intervention have explored the potential effects of extensive cognitive remediation on improving cognitive and psychosocial functioning in prodromal patients or the potential to prevent transition to psychosis.

Cognitive dysfunctions and cognitive remediation in schizophrenia

It is well known that impairments in cognition are characteristic and pervasive in schizophrenia and significantly influence the functional outcome [14-16]. The cognitive and the associated functional impairments cause patients with schizophrenia to experience disturbances in areas such as independent living, social relationships, and educational attainment [15,17] and are a strong predictor of response to psychiatric rehabilitation [18].

Cognition encompasses neurocognitive and social cognitive processes, which are regarded as two distinct but interrelated domains [19]. Neurocognition can be defined as “processes of linking and appraising information. It includes abilities like speed of processing, attention, verbal and visual learning and memory, working memory as well as reasoning and problem solving” [20], whereas social cognition can be defined as “the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviours of others” [21]. It is hypothesised that social cognition acts as a mediator between neurocognition and functional outcome. Evidence for this hypothesis has been found in several studies [20,22-27]. These findings imply that social cognition is proximal to the patients’ everyday functioning. In this context social cognition can be seen as critical for the daily functioning of the patients (e.g., community functioning, interpersonal relationships, and ultimately quality of life) [28]. Building on this rationale we decided to target both neurocognition and social cognition in our trial.

A promising method to alleviate cognitive deficits is using cognitive remediation (CR). It can be defined as “a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization” [29]. In the most recent meta-analysis of CR in schizophrenia, Wykes et al. reviewed 40 trials. The effect of CR on cognition, functioning, and symptoms was assessed post-treatment and at follow-up. They demonstrated a significant positive effect in most cognitive domains [global cognition effect size 0.45 with 95% confidence interval (CI) = 0.31-0.59] and on functional outcomes (effect size 0.42 with 95% CI = 0.22-0.62). The effect appears to be durable (effect size 0.43 with 95% CI = 0.18-0.67). It is noted that the impact of CR on functional outcomes was significantly greater in studies also providing psychiatric rehabilitation [29]. This leads to the conclusion that CR seems an important and beneficial target of intervention in people with schizophrenia. Research indicates that CR is also effective in other severe mental illnesses [30,31].

Cognitive dysfunctions and cognitive remediation among people at ultra-high risk for psychosis

A clinical staging model of the cognitive deficits in schizophrenia has been proposed. It suggests that there is a cognitive decline between early stages of the illness, implying that the cognitive deficits become increasingly severe as the illness develops [32]. Most studies favour a neurodevelopmental model suggesting that the cognitive deficits are already established before illness onset and remain mostly stable during the illness [33,34].

There is an increasing body of evidence demonstrating that patients in the UHR state show significant deficits in multiple cognitive domains [35-38]. In their meta-analysis on cognitive dysfunctions in the UHR state, Fusar-Poli et al. found cognitive deficits associated with the UHR state in attention, verbal fluency, visual and verbal memory, working memory, and executive functioning [35]. An area of cognition that also has been found to be impaired in the UHR state is social cognition, which appears to be closely related to functional outcome [22,39]. Evidence shows that the cognitive deficits in UHR patients have a significant impact on their level of functioning [37,40], an even greater impact than symptom severity [22,37].

Reviewing the literature in the electronic databases (PubMed, EMBASE, Clinical Trials.gov, and WHO Trial database)
Portal) for studies related to the terms “cognitive remediation, prodromal psychosis, or ultra-high risk states” resulted in only two published studies that have examined the effect of CR on UHR patients. Bechdolf et al. offered CR as part of a broader integrated intervention programme [9]. They found a beneficial effect of the integrated intervention, but it was not possible to isolate the effect of the CR. A pilot study by Rauchensteiner et al. compared the effectiveness of CR in 10 UHR patients to that of CR in 16 patients with schizophrenia and found relatively greater improvements in cognitive functioning (improved long-term memory functions as well as attention) in the former group [41]. However, as the authors also state, this finding needs to be replicated in studies using larger sample sizes. Furthermore, the observational design generally hinders fair assessment of the benefits of interventions [42]. Of note, the two studies included short-term remediation programmes (10-12 sessions) without direct assessment of the effect on daily functioning. Accordingly, there is a need for randomised clinical trials that apply more extensive cognitive training on larger UHR samples.

The aim of the FOCUS trial is to investigate to what extent CR may improve cognitive abilities and the associated psychosocial function in patients at UHR for psychosis. Bearing in mind the disabling consequences of cognitive deficits in schizophrenia and psychosis-like states, it seems vital to target these deficits to improve the everyday functioning of the patients. Knowing that the cognitive deficits manifest themselves in the UHR state, we expect that cognitive deficits may be even more amenable to treatment at this early stage of illness than what has previously been found at a more chronic stage [43,44]. Accordingly, targeting cognitive dysfunctions in the prodromal phase of psychosis may be the optimal time to intervene.

If a beneficial effect of CR on the cognitive and psychosocial dysfunctions in UHR patients is found, this would point to future randomised clinical trials and later potential implementation of CR in facilities offering early intervention in psychosis in order to enhance the ability of patients to function in their daily life.

**Hypotheses**

In the present study we will examine whether:

1. Cognitive remediation therapy will be superior to standard treatment in improving cognitive functioning in UHR patients (null hypothesis: no difference between the two intervention groups).
2. Cognitive remediation therapy will be superior to standard treatment in improving psychosocial functioning and clinical symptoms in UHR patients (null hypothesis: no difference between the two intervention groups).

**Methods**

**Recruitment**

The FOCUS trial is a randomised, blinded, parallel-group superiority clinical trial, enrolling a total of 126 help-seeking patients from in- and outpatient facilities in the catchment area of Copenhagen (Figure 1). Patients meeting standardised ‘at-risk’ criteria based on the Comprehensive Assessment of At-Risk Mental States (CAARMS) [45] will be approached about participating in this clinical trial. Patients will be randomised (1:1) to intensive CR plus standard treatment versus standard treatment, as described in further detail in the section Interventions.

**Inclusion criteria**

Participants aged 18-40 years who provide written informed consent and fulfil criteria for being at UHR for psychosis (defined by one or more of the following):

- Vulnerability (Trait and State Risk Factor) Group: Individuals with a combination of a trait risk factor (schizotypal personality disorder or a family history of psychotic disorder in a first degree relative) and a significant deterioration in functioning or sustained low functioning during the past year.
- Attenuated Psychotic Symptoms (APS) Group: Individuals with sub-threshold (intensity or frequency) positive psychotic symptoms. The symptoms must have been present during the past year.
- Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group: Individuals with a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within 1 week. The symptoms must have been present during the past year.

**Exclusion criteria**

Exclusion criteria are: a past history of a treated or untreated psychotic episode of 1 week’s duration or longer, psychiatric symptoms that are explained by a physical illness with psychotropic effect or acute intoxication (e.g., cannabis use), a diagnosis of a serious developmental disorder (e.g., Asperger’s syndrome), currently receiving methylphenidate, or rejects providing informed consent.

An exit criterion is transition to psychosis. Participants who convert to psychosis will be assessed with the 12-month assessment battery.
Interventions

**Cognitive remediation (CR) in the experimental group**

The CR is conducted in a group setting using both computerised exercises and group exercises. Patients assigned to the experimental intervention group will receive 2 h of CR (1 h of neurocognitive training and 1 h of social cognitive training) once a week for a total of 24 weeks. The training is done in an open group format. In addition to the group training there will be a total of 12 individual sessions of about 50 min aiming at maximising the bridging of the cognitive training to the everyday functioning of the patients, as well as working with individual goals.

The CR is delivered by a cognitive specialist in collaboration with a psychology student with knowledge of cognitive psychology. There will be a maximum of eight participants in each group; thus the therapist-to-patient ratio will be 1:4 or less.

If a patient meets the exit criterion “transition to psychosis”, he or she will be excluded from the intervention but still participate in assessments and statistical analyses, in accordance with the intention-to-treat principle.

**The neurocognitive training**

The neurocognitive remediation will be done by using the Neuropsychological Educational Approach to Cognitive Remediation (NEAR) [46,47]. NEAR is an evidence-based approach that focuses on aspects such as learning and motivation when doing CR. The patients will receive individual neurocognitive training on a computer followed by a group discussion that aims at relating the cognitive exercises to real-world activities. In addition to the group training the patients are instructed to do at least 1 h per week of computerised training at home.

**The social cognitive training**

The overall aim of the social cognitive training is to enhance the skills that enable the patients to understand the thoughts and intentions of others and to respond...
adequately in social situations. The social cognitive training will be by use of the Social Cognition and Interaction Training (SCIT) manual developed by Roberts et al. [48], which takes the form of group psychotherapy and skills training. It addresses several of the key social cognitive domains, comprising intolerance of ambiguity, attributional biases in explaining negative events, theory of mind (ToM), and emotion perception abnormalities. It is the assumption that these social cognitive skills hinder adequate social behaviour in schizophrenia and psychosis-like states.

**Individual sessions**
The individual sessions serve the purpose of maximising the transfer of the effect of the group training to the daily lives of the patients. The individual sessions are embedded in cognitive behavioural therapy (CBT) and use core CBT techniques such as goal setting, modifying distorted thinking, problem solving, and role-play. The content of the individual sessions will be tailored to fit the specific problems of the patient. The sessions will follow a manual that frames the sessions. However, it must be taken into account that the sessions cannot be completely manualised as the therapist approach and CBT techniques used will depend on the individual problem.

**Fidelity to treatment manual**
The intervention is manual-based, which improves standardisation of the treatment. David Roberts, co-author of the SCIT manual [48], has given a training course at the Mental Health Centre Copenhagen to ensure a proper understanding and use of the SCIT manual as well as adherence to it. The therapists will be offered bi-weekly Skype supervision from Dr Roberts throughout the trial.

A selected number of group sessions will be videotaped and used to rate adherence to the treatment manual by independent raters. The adherence will be rated by use of the SCIT Fidelity Scale (appendix in the SCIT manual) [48].

**Standard intervention in the experimental group**
The standard intervention in the experimental group is planned to be similar to the standard intervention in the control group (see description below).

**Standard interventions in the control group**
Patients allocated to the control group are free to choose whatever standard treatment they are offered by the clinicians managing their treatment. Usually standard treatment consists of a somewhat regular contact to health professionals in the in- and outpatient facilities in the capital region of Denmark (e.g., community psychiatric centres or private specialists in psychiatry). It involves monitoring of psychopharmacological treatment and different kinds of supportive counselling, e.g., concerning their psychiatric symptoms, relating to functional domains, or a more regular psychotherapeutic intervention depending on the nature of the health-service managing their treatment. In contrast to the intervention group, standard treatment does not involve specific cognitive training.

The standard treatment provided to both the experimental and control group will be carefully registered in retrospect at the end of the trial by an independent blinded assessor using a checklist comprising items such as use of medication, psychological interventions, number of sessions, and therapist skills.

**Medications**
Patients in both treatment groups are allowed to receive medication. In case an antipsychotic-naïve patient develops psychosis during the trial, this will be reported to the health service managing the treatment in order for them to initiate antipsychotic treatment.

**Assessments**
Assessments will be conducted at baseline, prior to randomisation, as information from the baseline assessment is used to perform stratified randomisation and validate inclusion and exclusion criteria. The assessments will be performed at cessation of treatment 6 months after randomisation and at follow-up 12 months after randomisation.

**Diagnosis**
The Comprehensive Assessment of At-Risk Mental States (CAARMS) [45] is used to classify patients as being at UHR for psychosis as well as assessing for transition to psychosis during the trial period. The Structured Clinical Interview for DSM-IV (SCID) [49,50] will be used to assess diagnosis.

The CAARMS is a validated instrument showing good to excellent reliability [45].

**Neurocognitive function**
Neurocognitive function will be assessed using a comprehensive test battery including the Danish Adult Reading Test (DART), a Danish adaptation of the National Adult Reading Test [51]; four subtests from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [51]; Vocabulary, Similarities, Block Design and Matrix Reasoning; the Brief Assessment of Cognition in Schizophrenia (BACS) battery [52]; and the Behavior Rating Inventory of Executive Functions-Adult Version (BRIEF-A) [53]. Furthermore, patients will undergo the following computerised tests from the Cambridge Neuropsychological
Test Automated Battery (CANTAB) [51]: Motor Screening Test, Spatial Span, Spatial Working Memory, Emotion Recognition Task, Stockings of Cambridge, IED Set Shifting Test, Paired Associate Learning, 5-Choice Serial Reaction Time, and Rapid Visual Information Processing.

The BACS is specifically designed to detect cognitive changes in response to treatment. The validity and reliability properties of the BACS have been established in patients with schizophrenia and healthy controls, and the BACS composite score has proven high test-retest reliability, increasing the likelihood of detecting a treatment-related effect [52,54,55].

The tests included in the CANTAB battery have proven high validity [56,57]. The reliability of the CANTAB tests varies between individual tests. High reliability ($r > 0.8$) has been shown on measures of visual processing, e.g., the Paired Associates Learning task, while lower reliability has been found particularly on measures of executive functions, e.g., sub-measures of the IED Set Shifting Task [58]. This lower reliability of tests that assess executive functions is very difficult to avoid because of the necessary task novelty involved in assessing executive processing [58].

Social cognitive function

Social cognitive function will be measured with The Awareness of Social Inference Test (TASIT) [59], the High-Risk Social Challenge task (HiSoC) [60], the Social Cognition Screening Questionnaire (SCSQ) [61], and Social Responsiveness Scale (SRS) [62].

Symptomatology

General symptomatology, negative, depressive, and manic symptomatology will be measured with the Brief Psychiatric Rating Scale Expanded Version (BPRS-E) [63], the Scale for the Assessment of Negative Symptoms (SANS) [64,65], the Montgomery-Åsberg Depression Rating Scale (MADRS) [66], the Young Mania Rating Scale (YMRS) [67], and the Clinical Global Impression (CGI) [68]. Nine cognitive-perceptive basic symptoms from the Schizophrenia Prediction/Proneness Instrument-Adult Version (SPI-A) [69] will be used as a measure of subjectively experienced cognitive-perceptive symptoms.

Psychosocial function

Three measures will be included to assess psychosocial functioning: the Personal and Social Performance Scale (PSP) [70], Social and Occupational Functioning Assessment Scale (SOFAS) [71], and Global Functioning: Social and Role Scales [72].

Other assessment tools

Five other assessment tools will be used assessing family history, premorbid functioning, substance use, and quality of life. An abbreviated version of the Family Interview for Genetic Studies (FIGS) Family History Index (FHI) (Maxwell M.E: Family interview for genetic studies (FIGS); Manual for FIGS. Unpublished manuscript) is used to assess family history of psychiatric disorder, the Premorbid Adjustment Scale (PAS) [73] assessing premorbid functioning level, Alcohol Smoking & Substance Involvement Screening Test (ASSIST) (WHO ASSIST working group 2002 [74]) assessing substance use, and Quality of Life Scale (QOLS) [75] assessing the patients’ perceived quality of life. At cessation of treatment after 6 months the patients’ satisfaction with the received treatment will be evaluated using the Client Satisfaction Questionnaire (CSQ) [76].

Adverse events

The participants’ well-being will be a primary focus during the trial. Accordingly, their safety will be monitored and accurately reported throughout the treatment period. CR is not known or expected to cause adverse events [77]; therefore, we do not expect any adverse events to occur. However, should an adverse event occur, it will be dealt with properly by the therapists in charge of the treatment. Using our outcome instruments we will investigate whether the FOCUS intervention causes nominally worse scores, which will be interpreted as a possible indication of harm.

Setting of assessment

All the assessments will take place at the Mental Health Centre Copenhagen. Most tests are assessed using paper and pencil with the exception of CANTAB, which is a computerised test battery, and the HiSoC test, which uses videotaping. The staff members performing the SCID interview are psychologists and medical doctors who have undergone a 4-day training course using the SCID diagnostic interview co-supervised by Dr Joseph Ventura.

Data management

All the data will be stored in locked cabinets at the Mental Health Centre Copenhagen under blinded conditions (see Blinding).
Outcomes and sample size calculation

Primary outcome
The primary outcome is overall cognitive function, measured with the BACS composite score 6 months after randomisation.

Sample size calculation
The sample size calculation is based on our primary outcome, a priori defined to be the between-group difference at 6 months on the BACS composite score. We consider a clinically relevant difference on this scale to correspond to a Cohen’s $d$ of 0.50 (e.g., assuming a between-group difference of 3.0 and a pooled SD of 6.0) [29]. With a two-sided alpha of 0.05 and power of 80%, this will require 63 participants to be randomised to each of the two interventions.

Secondary outcomes and power calculations
The difference in global personal and social functioning 6 months after inclusion will be measured with the PSP. With 63 participants in each group, and assuming a pooled standard deviation of 10 points [72,78-81], we will have more than 97% power to detect a difference of 7 points between the groups, which would be considered the minimal clinically relevant difference on this scale [82].

The BPRS-E will be used to measure symptomatology (e.g., psychosis-like symptoms). The BPRS scale is expected to have a pooled standard deviation of 20.0 points [83]. Given a sample size of 63 per group and a two-sided alpha of 0.05, we have 80% power to detect a difference between the two groups of at least 10.06 points. Antipsychotic treatment and psychotherapeutic interventions have been shown to reduce BPRS by more than 12 points [5,84], indicating that we have sufficient power to detect the minimally relevant difference on this secondary outcome.

Negative symptomatology will be assessed using the SANS. The SANS scale is expected to have a pooled standard deviation of 13 points [5]. Given a sample size of 63 per group and a two-sided alpha of 0.05, we have 80% power to detect a difference between the two groups of at least 6.54 points. Treatments with cognitive and supportive therapy as well as risperidone have been shown to reduce SANS by more than 7 points [5]. This indicates that we have sufficient power to detect the minimally relevant difference of this secondary outcome.

Depressive symptoms will be assessed using the MADRS. Data from a previous randomised clinical trial with UHR patients shows a SD of 9.56 points [6]. Allowing for larger variance in data we set a SD of 10 when calculating detectable differences. With our sample size of 63 per group and a two-sided alpha of 0.05, we have 80% power to detect a difference between the two groups of at least 5.03 points.

Exploratory outcomes
Exploratory outcomes will be transition to psychosis assessed by the CAARMS; symptomatology assessed by the CAARMS and SPI-A; and social cognition assessed by the ERT, TASIT, HiSoC, SCSQ, and SRS. Psychosocial function will be measured with the SOFAS and Global Functioning: Social and Role Scales. Additionally, the BRIEF-A will be used as a proxy measure of daily functioning. Patients perceived quality of life will be assessed with the QOLS, and lastly the number of participants experiencing adverse events will be recorded.

Randomisation
Randomisation will be centralised with a concealed randomisation sequence carried out by the Copenhagen Trial Unit (CTU). Randomisation will be stratified by current use of antipsychotic medication (yes/no) and the IQ score ($\leq 100/\geq 100$). Block size will be unknown to the investigators and clinicians.

Signed informed consent will be obtained prior to randomisation. The randomisation is computerised and central. The blinded assessors will enter the participant’s data on a webpage hosted by the CTU. Thereafter, a computerised randomisation is performed, and an email is sent to an independent member at Mental Health Centre Copenhagen revealing to which intervention programme the participant has been allocated. The staff member then contacts the participant and informs him or her of the result of the randomisation. The randomised intervention allocation is concealed until the statistical analyses of resulting data have been completed.

Blinding
The patients and treatment providers will not be blinded. The blinding applies to researchers involved in assessments, data management, data analysis, and drawing outcome conclusions. For the follow-up interviews the patient is instructed in advance not to reveal what type of treatment was received.

Statistical analyses
The planned comparisons between the two groups on continuous outcomes will be carried out with a generalised linear model adjusted for stratification variables, potential baseline imbalances, and skewed attrition, with missing data handled by multiple imputations. As an important secondary assessment of this type of outcome, linear mixed model analyses with repeated measurements and an unstructured covariance matrix will assess the interaction term between time and intervention. For non-normally distributed continuous outcome measures, non-parametric analyses will be applied. For dichotomous outcomes, logistic regression will be applied, and for time to transition, Cox proportional hazards regression.
will be applied. All analyses will be according to the intention-to-treat principle, analysing all participants in the groups they were assigned to by randomisation. We expect to encounter missing data, and this will be handled with the linear mixed models and multiple imputations as appropriate. A blinded and independent statistician who has no contact to the trial participants will conduct the primary efficacy analyses.

**Ethical consideration**

The trial has obtained approval by the Regional Ethics Committee of Zealand (H-6-2013-015) and the Danish Data Protection Agency (RHP-2014-009-02670). The trial is registered at ClinicalTrial.gov as NCT 02098408. Positive as well as neutral and negative results of the trial will be published in international journals.

The participants will receive information on the trial both verbally and in written form. Written informed consent will be obtained from each participant before inclusion in the trial. It is emphasised that participation in the trial is voluntary and that the participant can withdraw his or her consent at any time without consequences for treatment possibilities. We will upload depersonalised individual patient data to be used in meta-analyses on Zenodo via OpenAIRE (https://www.openaire.eu/).

**Discussion**

There are several strengths in the design of the FOCUS trial. First, to our knowledge no other randomised clinical trial has assessed the effect of both neurocognitive and social cognitive remediation in a UHR population. Second, the CR has a primary focus on linking cognitive remediation to real-life improvements. Third, it is a large-scale trial. As UHR patients are difficult to attain, the sample size of 126 UHR patients makes it one of the biggest UHR intervention trials to date. Fourth, it employs observer-blinded assessment of outcomes with the intention to ensure that the outcome data are assessed without bias [85]. Moreover, data management, data analyses, and conclusions will be conducted and drawn blind to the intervention group. Fifth, assessing outcome at cessation of treatment after 6 months will allow evaluating the immediate effect of the CR, whereas the 12-month follow-up evaluates the long-term effects of the CR intervention. Sixth, the wide range of outcome estimates in the trial allows the opportunity to assess outcome in multiple areas of cognition, symptomatology, and adaptive functioning.

The trial may have some limitations as to the best of our knowledge no published trial has investigated the effect of combining the SCIT treatment with a neurocognitive remediation programme. Hence, we lack knowledge on the feasibility of this approach. However, as stated in the Background section, evidence shows that both the neurocognitive and social cognitive domains are impaired in UHR patients. Therefore, it seems essential to try to target both domains. This is further supported by the hypothesis that social cognition acts as a mediator between neurocognition and real-world outcome. Furthermore, it seems highly effective to combine treatment modalities in CR [29,86]. Another limitation is that the experimental intervention is an add-on to standard treatment. This design could potentially cause the problem of patients in the intervention group receiving less standard treatment as a result of participating in the trial.

**Trial status**

Trial initiation was April 2014. By November 2014, 19 patients had been randomised.

**Abbreviations**

CR: Cognitive remediation; CTU: Copenhagen trial unit; SCIT: Social cognition and interaction training; RCT: Randomised clinical trial; ToM: Theory of mind; UHR: Ultra-high risk.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

LBG, MN, BF, and LR conceived the trial. LBG and MN wrote the first draft of the protocol. CG participated in the design of the trial, writing the manuscript, and critical revision of the work. GW and KK participated in the design of the trial, writing the manuscript, and critical revision of the work, and were involved in the data collection. BF, LR, and AV contributed with expertise in cognitive deficits and cognitive remediation and participated in the design of the trial, writing the manuscript, and critical revision of the work. AM and DR contributed with expertise in cognitive remediation and the design of the intervention, writing the manuscript, and critical revision of the work. CRH contributed with statistical expertise, writing the manuscript, and critical revision of the work. All authors read, improved, and approved the final manuscript.

**Acknowledgements**

Funding for this trial was provided by Mental Health Services of the Capital Region of Denmark, the Research Fund of the Capital Region Denmark, and the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS. The funding sources had no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The authors would like to thank Jens Richardt Møllegaard Jepsen (MSc Psychology, PhD) and Vibeke Fuglsang Bliksted (MSc Psychology, PhD) for their consultative expertise on social cognition during the design phase, Maria Galsgaard (BA Psychology) for her participation in implementing the CR in the trial, Heidi Dorthe Jensen (research nurse), Hanne Junge Larsen (secretary), and Merete Carlsen (laboratory technician) for their help with the practicalities of the trial, and Tina Dam Kristensen (MSc Psychology) for her help with the data collection and input for the trial.

**Author details**

1 Mental Health Centre Copenhagen, Copenhagen University Hospital, DK-2400 Copenhagen, Denmark. 2 Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, DK-2600 Glostrup, Denmark. 3 Centre for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Centre Glostrup, Copenhagen University Hospital, DK-2600 Glostrup, Denmark. 4 Centre for Rehabilitation for Brain Injury, DK-2300 Copenhagen, Denmark. 5 Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Righospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark. 6 Columbia University Medical Center, New York, NY 10032, USA. 7 Department of Psychiatry, Division of Schizophrenia and
Related Disorders, University of Texas Health Science Center, San Antonio, TX 78229, USA.

Received: 3 October 2014 Accepted: 23 December 2014
Published online: 27 January 2015

References
1. McGrath J, Saha S, Chant D, Welham J (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67–76
2. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schulze-Lutter F et al (2013) The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70:107–20
3. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR et al (2013) Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. Schizophr Res 149:56–62
4. McGorry PD, Yung AR, Phillips LL, Yuen HP, Francey S, Cosgrove EM et al (2002) Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 59:921–8
5. McGorry PD, Nelson B, Phillips LL, Yuen HP, Francey SM, Thampli A et al (2013) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. J Clin Psychiatry 74:349–56
6. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW et al (2006) Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 163:700–9
7. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harigg SM et al (2018) Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 67:146–54
8. Nordenfelt M, Thorup A, Petersen L, Oihenschlaeger J, Melas M, Christensen TD et al (2006) Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment. Schizophr Res 83:29–40
9. Bechdolf A, Wagner M, Ruhmann S, Harrigan S, Putzfeld V, Pukrop R et al (2012) Preventing progression to first-episode psychosis in initial prodromal states. Br J Psychiatry 200:22–9
10. Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J et al (2004) Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. Br J Psychiatry 185:291–7
11. Morrison AP, French P, Stewart SL, Birchwood M, Fowler D, Gunnely Al et al (2012) Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 344:e2233
12. Addington J, Epstein L, Liu L, French P, Boydell KM, Zipursky RB (2011) A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. Schizophr Res 125:54–61
13. van der Gaag M, Nieman DH, Rietdijk J, Dragt S, Ising HK, Klaassen RM et al (2010) Long-chain omega-3 fatty acids for indicated prevention of psychosis: a randomised placebo-controlled trial in ultra-high-risk individuals. Lancet 375:1983–90
14. Bellack AS, Gold JM, Buchanan RW (1999) Cognitive rehabilitation for schizophrenia: problems, prospects, and strategies. Schizophr Bull 25:257–74
15. Green MF, Kern RS, Braff DL, Mintz J (2000) Neuropsychological deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 26:119–36
16. Wykes T, Spaulding WD (2011) Thinking about the future cognitive remediation therapy—what works and could we do better? Schizophr Bull 37(Suppl 1):S90–50
17. Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–30
18. McGurk SR, Twamley EW, Sitzer DJ, McHugh GJ, Mueser KT (2007) A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 164:1791–802
19. Fett AK, Veichbauer W, Dominguez MD, Perkins DL, van Os L, Kabbaband L (2011) The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev 35:573–88
20. Schmidt SJ, Mueller DR, Roder V (2011) Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. Schizophr Bull 37(Suppl 1):541–54
21. Green MF, Penn DL, Bentall R, Carpenter WT, Gaebel W, Gur RC et al (2008) Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. Schizophr Bull 34:1211–20
22. Bartholomew CF, Allott K (2012) Neurocognitive and social cognitive approaches for improving functional outcome in early psychosis: theoretical considerations and current state of evidence. Schizophr Res Treat 2012:815315
23. Addington J, Saeed H, Addington D (2006) Facial affect recognition: a mediator between cognitive and social functioning in psychosis? Schizophr Res 85:142–50
24. Addington J, Saeed H, Addington D (2006) Influence of social perception and social knowledge on cognitive and social functioning in early psychosis. Br J Psychiatry 189:373–8
25. Horton HK, Silverstein SM (2008) Social cognition as a mediator of cognition and outcome among deaf and hearing people with schizophrenia. Schizophr Res 105:125–37
26. Niemow TM, Docherty NM, Cohen AS, Dinzeo TJ (2006) Attentional dysfunction, social perception, and social competence: what is the nature of the relationship? J Abnorm Psychol 115:408–17
27. Vaskinn A, Sundet K, Feli S, Simonsen C, Birkenaes AB, Jonsdottir H et al (2008) Emotion perception and learning potential: mediators between neurocognition and social problem-solving in schizophrenia? J Int Neuropsychol Soc 14:279–88
28. Couture SM, Perlin DL, Roberts DL (2006) The functional significance of social cognition in schizophrenia: a review. Schizophr Bull 32(Suppl 1):544–63
29. Wykes T, Huddy V, Cellard C, McGurk SR, Cozob P (2011) A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry 168:472–85
30. Lewandowski KE, Eack SM, Hogarty SS, Greenwald DP, Keshavan MS (2011) Is cognitive enhancement therapy equally effective for patients with schizophrenia and schaizoaffective disorder? Schizophr Res 125:291–4
31. Deckersbach T, Nerenberg KA, Kessler R, Lund HG, Amnetranom RM, Sachs G et al (2010) RESEARCH: Cognitive rehabilitation for bipolar disorder: An open trial for employed patients with residual depressive symptoms. CNS Neurosci Ther 16:298–307
32. Lewandowski KE, Cohen BM, Ongr D (2011) Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med 41:225–41
33. Bozikas VP, Andreou C (2011) Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. Aust N Z J Psychiatry 45:93–108
34. Bora E, Murray RM (2014) Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr Bull 40(4):744–55
35. Fusar-Poli P, Deste G, Smieskova R, Baralt S, Yung AR, Howe O et al (2012) Cognitive functioning in prodromal psychosis: a meta-analysis. Arch Gen Psychiatry 69:562–71
36. Hawkins KA, Addington J, Keefe RS, Christensen B, Perkins DO, Zipurksy R et al (2004) Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res 67:115–22
37. Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewry R, O'Brien M et al (2006) Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr Res 84:100–11
38. Brewer WJ, Wood SJ, Phillips LJ, Francry SM, Pantelis C, Yung AR et al (2006) Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull 32:538–55
39. Thompson AD, Bartholomew C, Yung AR (2011) Social cognition deficits and the 'ultra high risk' for psychosis population: a review of literature. Early Interv Psychiatry: 5:192–202
40. Lin A, Wood SJ, Nelson B, Brewer WJ, Spiolatocopoulos D, Bruener A et al (2011) Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. Schizophr Res 132:1–7
41. Rauensteiner S, Kowohl W, Ozgorral S, Littmann E, Gudowisky Y, Wittma H et al (2011) Test-performance after cognitive training in persons at risk mental state of schizophrenia and patients with schizophrenia. Psychiatry Res 185:334–9
62. Bolte S, Poustka F, Constantino JN (2008) Assessing autistic traits: cross-cultural pitfalls of CANTAB. Eur Psychiatry 22:104–9
63. Lowe C, Rabbit P (1998) Test-re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge Neuropsychological Test Automated Battery. International Study of Neuropsychological Test Automated Battery. International Study of
64. Barnett JH, Robbins TW, Leeson VC, Sahakiana BJ, Joyce EM, Blackwell AD (2007) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the late—and additional memory dysfunction in the late–prodromal state. Schizophr Bull 33:868–70
65. Andreasen NC (1984) Scale for the assessment of negative symptoms. SANS. Dept. of Psychiatry, College of Medicine, the University of Iowa, Iowa City, Iowa
66. Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–9
67. Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:29–35
68. Guy W (1976) ECDEU Assessment Manual for Psychopharmacology - Revised (DHHS Publ No. ADM 76-338). In: Rockville, MD. US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs., pp 218–22
69. Schulze-Lutter F, Ruhrmann S, Fusar-Poli P, Bechdolf A, Schimmelmann BG, Nolteleker J (2012) Basic symptoms and the prediction of first-episode psychosis. Curr Pharm Des 18:351–7
70. Morosini PL, Magliano L, Brambilla L, Ugozzi S, Piai R (2000) 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 101:323–9
71. Hilsenroth MJ, Ackerman SJ, Blagys MD, Baumann BD, Baity MR, Smith SR (2000) Reliability and Validity of DSM-IV Axis V. Am J Psychiatr 157:1858–63
72. Combatt BA, Aufer AM, Naegele CE et al (2007) Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophr Bull 33:868–70
73. Cannon-Spoor HE, Potkin SG, Wyatt RJ (1982) Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 8:470–4
74. World Health Organisation ASSIST Working Group (2002) The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 97:1183–1194
75. Heinrichs DW, Hanlon TE, Carpenter WTJR (1984) The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 10:388–98
76. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD (1979) Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann 2:197–207
77. Klingberg S, Herrlich J, Wiedermann G, Wolwer V, Meinsner C,Engel C et al (2012) Adverse effects of cognitive behavioral therapy and cognitive remediation in schizophrenia: results of the treatment of negative symptoms study. J Neu Ment Dis 2005:569–76
78. Brewster WJ, Francyre SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ et al (2005) Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry 162:71–8
79. Becker HE, Nieman DH, Wittink S, Dingemans PM, van de Fliert JR, Verhoeff E et al (2010) Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration? Psychol Med 40:599–606
80. Frommann I, Pukrop R, Brinkmeyer J, Bechdolf A, Ruhrmann S, Bering J et al (2011) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early–and additional memory dysfunction in the late–prodromal state. Schizophr Bull 37:861–3
81. Eastwood AD, Heaton RK, Cadenhead KS (2007) Neurocognitive deficits in the (putative) prodrome and first episode of psychosis. Schizophr Res 93:266–77
82. Nasrallah H, Morosini P, Gagnon DD (2008) Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. Psychiatry Res 161:213–24
83. Ballerini A, Boccolani R, Conomoppi C, Casacchia M, Margari F, Minervini L et al (2007) An observational study in psychiatric acute patients admitted to General Hospital Psychiatric Wards in Italy. Ann Gen Psychiatr 6:2
84. Lepping P, Sambhi RS, Whitton P, Lane S, Poole B et al (2011) Clinical trial: in vitro: evidence of findings in trials of antipsychotics: systematic review. Br J Psychiatr 198:341–5
85. Savovic J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J et al (2012) Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med 157:429–38
86. Eack SM, Greenwald DP, Hogarty SS, Cooley SJ, DiBany AL, Monteiro DM et al (2009) Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. Psychol Serv 60:1468–76