Author's response to reviews

Title: 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

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Author's response to reviews: see over
Reviewer’s report

Abstract

1. Please include the aims/objectives of the study in the abstract and the trial acronym.

Response: The aims of the study and the trial acronym have now been included in the abstract.

Background

2. Please define and introduce the constructs in this manuscript (e.g., prodromal intervention, psychosis [and prevalence], social cognition, neurocognition, cognitive remediation) as the broader public of readers may need to be educated about these constructs.

Response: The constructs of prodromal intervention, psychosis, social cognition, neurocognition, and cognitive remediation are now described in the background section.

3. The background could be improved (would be stronger) if the scientific and clinical relevance is more clearly described.

Response: The relevance of the study is now highlighted in the background section:

“The aim of this trial is therefore 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 [42, 43]. 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”.

4. Please include hypotheses/objectives to the manuscript and trial design.

Response: The hypotheses of the study are now included in the manuscript:

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 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 groups).

Methods

5. Please describe the method of delivery of assessments (eg. Paper pencil/online, location of assessment) and SCID) background and training of assessors and psychometric properties of all measurements.

Response: The method of delivery of assessment and background and training of SCID assessors are now described.

Regarding the psychometric properties of the instruments, we have now added a detailed description of the psychometric properties (validity and reliability) of the instruments CANTAB, BACS and CAARMS that are the most important outcome measures in the trial. We think that more detailed information about the psychometric properties of all sub-measures would be too comprehensive to include, but we will be happy to do so, if the editor asks us to include this information.

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

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 due to the necessary task novelty involved in assessing executive processing [58]. “

6. Please include information about data management and harms (see Spirit guidelines)

Response: This is now described in more detail in the section “adverse events” and we have added the paragraph “Data-management”.

Background

1. Please add statistics to the sentence ‘in the most recent meta-analysis on prodromal interventions...’ to be more informative.
Response: This has now been described in further detail in the manuscript:

“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% confidence interval (CI = 0.22-0.62). The effect appears to be durable (effect size 0.43 with 95% confidence interval (C) =0.18-0.67)”.

2. Social cognition is hypothesized to act as a mediator between Neurocognition and functional outcome. Has this been investigated previously?

Response: This is now described in further detail in the manuscript:” 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]”.

Note: Due to time constraints in the trial, the outcome measure SCoRS has been excluded. It has therefore been removed from the manuscript.