Author’s response to reviews

Title: Erythropoietin as an add-on treatment for cognitive side-effects of electroconvulsive therapy: a study protocol for a randomized controlled trial

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Reviewer reports

RE: TRLS-D-17-00911

Title: Erythropoietin as an add-on treatment for cognitive side-effects of electroconvulsive therapy: a study protocol for a randomized controlled trial

Reviewer #1

Thanks you for asking me to review this well written protocol on a novel trial of erythropoietin in the treatment of post ECT cognitive changes. I have two main comments.
1.A. First is that the relevance of the authors previous work in this field is not clearly described. Could the authors describe in more details their previous work with erythropoieten and the relevance to this study.

We thank the reviewer for raising this relevant point. In response to this, we have now described in more detail our findings regarding the effects of erythropoietin (EPO) on cognitive impairments in mood disorders and their relevance for the present trial:

Background, p. 3-4:

“Randomized controlled clinical studies suggest that 8-12 weeks of systemically administered high-dose (40,000-48,000 IU) EPO improves attention, memory, and executive functions in patients with treatment-resistant depression (TRD) (9), bipolar disorder (BD) (8), multiple sclerosis (15), or schizophrenia (16). The cognitive benefits of EPO treatment seem to result from direct neurobiological actions rather than non-specific changes in red blood cells. For example, randomized placebo-controlled functional magnetic resonance imaging (fMRI) studies by our group (17, 18) showed that a single high-dose (40,000 IU) EPO- vs. placebo enhanced memory-relevant prefrontal and hippocampal activity in healthy and depressed individuals without affecting red blood cells. Consistent with this, our subsequent randomized, placebo-controlled trials revealed that 8 weekly infusions of high-dose (40,000 IU) EPO vs. saline had mood-independent beneficial effects on cognitive function in patients with TRD (N=40) and BD in remission (N=44) (8, 9). These cognitive benefits were accompanied by EPO-associated increase in neural activity within the frontal and the parietal lobes during strategic encoding and working memory tests (8, 9, 19).” (…) Importantly, these brain changes were independent of changes in mood and lasted long-term beyond red blood cell normalization. Several neurobiological actions may underlie these beneficial cognitive effects of EPO treatment, including activation of anti-inflammatory, anti-apoptotic, and antioxidant signaling pathways (14, 22, 23) and growth of dendrites, maturation of neural progenitor cells and upregulation of brain-derived neurotrophic factor (BDNF) (24, 25). (…) This trial extends our previous work by investigating for the first time whether adjunctive EPO treatment can counteract the cognitive side-effects of ECT.”

Outcome assessments, p. 8: “We have found an improvement on this ‘speed of complex cognitive processing’ composite measure in our previous EPO cognition trial across BD and TRD patients after 8 weeks of weekly EPO treatment (31). In the present study, we therefore include the same global cognition score as the primary outcome measure. This consisted of the
following six neuropsychological tests, spanning verbal memory, attention, and executive functions:

• Added reference:


1.B. The authors refer for the first time in study feasibility to a previous RCT they did but it is not clear how this relates to the current study.

We thank the reviewer for raising this relevant point. We agree with the reviewer, that the relevance of this RCT is unclear and have now deleted this from the manuscript. We therefore reference only (a) the recruitment rate in our previous EPO trials (n=84 over 3 years) and (b) the estimated number of patients receiving ECT for non-psychotic depression at Psychiatric Centre Copenhagen (n=200 over 6 years) as a basis for our estimation that recruitment of 52 unipolar or bipolar disorder patients scheduled for ECT over 28 months is achievable. The following changes have been made to the manuscript:

Study feasibility, p. 12:

“Approximately 200 patients with non-psychotic unipolar disorder aged 18-60 years received ECT at Psychiatric Centre Copenhagen during a 6-year period from 2008-2014 (50). In our double-blinded randomized trials of the effects of 8-weeks EPO treatment, we included 84 patients with mood disorders over a 3 year-period (2009-2012) (8, 9). Given this and our collaboration with other hospitals within the Psychiatric Centre Copenhagen, we consider recruitment of 52 patients over 28 months for the present study feasible.”

• Added reference:

1. B continued. (...) This is made harder for the reader as the references seem to be out of order as they do not link with what is in the text - for example reference 24 is to a standard diagnostic instrument yet in the text it is supposed to refer to an RCT of 29 patients (which RCT and why is this relevant?).

We thank the reviewer for noticing the incorrect reference. We have now made sure that all references are in correct order and have replaced the wrong reference in “Study feasibility” (p. 12) with the correct references.

2. The second is the sample size. I could not replicate the authors calculation of sample size. Could the authors describe in more details how they calculate the composite cognitive score and their justification of choosing standard deviation of 0.5 - what does this mean clinically? My understanding of calculating sample size using the standard deviation is that readers also need to know the anticipated mean changes in scores between two time points as well as the standard deviation.

The authors thank the reviewer spotting this lack of clarity in the statistical power calculation. In response to this, we have now made a distinction between a clinically relevant differential change between groups in the composite score of 0.4 standard deviations, with a standard deviation of the mean change of 0.5. These numbers are in line with the recent recommendations by the International Society for Bipolar Disorders (ISBD) cognition task force (Miskowiak et al., Bipolar Disord., 2017) and similar to the findings from our previous EPO cognition trials in mood disorder patients (Ott et al., 2016, Eur Neuropsychopharmacol):

Sample size and power calculation, p.10: “The difference in cognitive change between EPO and the saline-treated groups from baseline to post-treatment in our previous trial was 0.5 SD. We estimate that a clinically relevant differential change in the cognitive composite score between EPO and placebo groups is 0.4 standard deviations (SD; corresponding to a moderate effect size), with a SD of the mean change of 0.5. This is consistent with the recommendations by the International Society for Bipolar Disorders (ISBD) cognition task force recommendations (48). Specifically, the task force noted that a differential change between groups of 0.2-0.4 SD on a global composite score may represent a clinically relevant change as this may translate into moderate to large functional improvement in patients with mood disorders (48). In our previous 8 weeks EPO trial, the difference between EPO and the saline groups regarding change in the
cognitive composite score from baseline to post-treatment was 0.5 standard deviations (31). Based on the ISBD task force recommendations and our previous findings regarding the effects of longer-term EPO treatment, the sample size of N=52 (n=26 per group) in the current trial will reach a ≥0.8 power to detect a similar clinically relevant differential change of 0.4 SD in the primary outcome measure (the cognitive composite score) with a SD of this change of 0.5 between the 2 groups at an alpha level of 5% (two-sided test) (31).”

• Added reference:


Additional changes made by the authors

(a) Due to recruitment difficulties, we have decided to implement the following change for the inclusion criteria, which is specified in the revised manuscript:

1. Extended the age range to ≤70 years of age as described in the methods section, page 5:

   “Eligible patients have a diagnosis of MDD unipolar disorder (UD) or BD with a current moderate to severe depressive episode symptoms, a Hamilton Depression Rating Scale 17-items (HDRS-17 (27) score ≥17), are 18-70 years of age, have fluent Danish skills and are able to provide informed consent.”

(b) To follow the recommended items to address in a clinical trial protocol (cf., SPIRIT 2013 Checklist), we have also outlined our plans for communicating potential, important protocol modifications. Furthermore, we have underlined that we will/have obtain(ed) informed consent from all participants in the study:

Ethical approval and consent to participate” section, p.17:

“Any important protocol modifications will be reported to the Danish Medicines Agency, the Ethics Committee in the Capital Region of Denmark, and the Danish Data Protection Agency.
Written informed consent has been and will be obtained from all participants. Written informed consent has been and will be obtained from all participants.”