

Elsevier Editorial System(tm) for The Lancet
Manuscript Draft

Manuscript Number:

Title: COBRA authors' response to correspondence of Dr Vieta and Mr Sanchez-Moreno.

Article Type: Invited Correspondence

Keywords: Behavioural Activation
Cognitive Behaviour Therapy
non-inferiority trial
depression

Corresponding Author: Prof. David A Richards, PhD

Corresponding Author's Institution: University of Exeter

First Author: David A Richards, PhD

Order of Authors: David A Richards, PhD; Finning Katie, BSc; Rod S Taylor, PhD

Manuscript Region of Origin: UNITED KINGDOM

COBRA authors' response to correspondence of Dr Vieta and Mr Sanchez-Moreno.

We thank Dr Vieta and Mr Sanchez-Moreno for commenting on our COBRA trial,(1) which demonstrated that behavioural activation (BA) can be delivered by junior mental health workers (MHWs) with no lesser effect than cognitive behavioural therapy (CBT) delivered by professional psychotherapists.

We acknowledge that in non-inferiority trials without a placebo arm there is a theoretical possibility of demonstrating that both treatments are equally ineffective(2). We suggest four *a priori* and one *post hoc* question to mitigate this possibility. 1) Has the control treatment been shown to be clinically effective in meta-analyses? 2) Is the control treatment routinely available to patients? 3) Does the untreated condition cause substantial morbidity, mortality and economic burden? 4) Is the planned post-randomisation follow up period substantial? Where the answer to these initial four questions is 'yes', it would be an example of 'research waste'(3) to randomize participants to a no-treatment arm in a non-inferiority trial, a placebo being both unnecessary and unethical. Finally, 5) Does the trial's control group outcomes compare favourably to meta-analytic results where effectiveness has been unequivocally demonstrated? If the answer to this final question is also 'yes', trialists can be reassured that demonstrating non-inferiority for an experimental treatment has clinical meaning. In our COBRA trial, the answer to all five questions was 'yes'. We do not agree that "the absence of a placebo intervention," and "the limited masking of the interventions" (impossible in most complex behavioural interventions) "leads to much lower methodological standards as compared to drug trials", nor do we agree that "Superiority is the only way to prove actual efficacy."

Words: 263

1. Richards DA, Ekers D, McMillan D, Taylor RS, Byford S, Warren FC, et al. Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial. *The Lancet*. 2016;388(10047):871-80.
2. European Agency for the Evaluation of Medicinal Products. Points to consider on switching between superiority and non-inferiority. London: EMEA, 2000.
3. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *The Lancet*. 2009;374:86-9.