

Title: Untrustworthy trials should be challenged if no satisfactory response is forthcoming: a response to Monticone

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We acknowledge Dr Monticone's letter in response to our paper [7] which investigated the trustworthiness of a group of studies published by his group. Contrary to Dr Monticone's suggestion, we made no accusation of data fabrication or misconduct. Rather, we raise valid concerns regarding the trustworthiness of this group of trials that we judge to be important, in particular because their inclusion in reviews and clinical guidance risks over-confidence and error. What caused these trial reports to be submitted and accepted for publication is beyond the scope of our investigation.

To address Dr Monticone's specific points:

- a) We acknowledged the limitations of Stouffer's method [2,9] in our paper. We ran and reported our analyses of baseline variables with and without categorical variables. Even in the latter analysis, omnibus p values diverged from what might be expected with randomisation in five of the ten included trials.
- b) We recognise and have corrected an error regarding the description of the normative data cohort [6]. Importantly, this does not alter our findings as we did not make any definitive risk judgements regarding the feasibility of participant characteristics.
- c) We are not aware of a clear theoretical or evidential basis that would predict much greater effectiveness of cognitive behavioural therapy (CBT) when added to exercise in the Italian context, compared with "Anglo-Saxon countries" and do not accept that the Italian setting of these trials offers a compelling explanation for the divergence of their results.
- d) The apparent suggestion that CBT added to rehabilitation may have delivered greater benefits when constituting a smaller proportion of the overall intervention is interesting. One potential reason we can acknowledge is the potential for additive effects when CBT is added to rehabilitation. However, we note that the results of the trials authored by Monticone and colleagues also diverge substantially from those of a review [8] that specifically focused on the addition of psychological treatments to physical treatments versus physical treatments alone.
- e) It is common to analyse the included outcomes as though they were from interval scales. Had we analysed the data as ordinal, we would have observed the same degree of divergence. Our findings are robust to any reasonable analytical approach.
- f) Though the Trustworthiness Screening Tool [6] has not been formally validated, it allowed us to take a consistent, systematic approach across trials and probes a range of reasonable questions regarding research governance and data authenticity.
- g) We raised concerns in our paper regarding the low levels of attrition in some of the studies, which are striking. Trials commonly employ methods to improve retention similar to those described by Dr Monticone, but often with markedly lower success.
- h) As for the points regarding ethics, we requested evidence of ethical approvals, study protocols and individual patient data. This correspondence was included in our submitted draft but was removed during the editorial process. Dr Monticone declined to share the requested information with us.
- i) Dr Monticone states in his letter that protocols were developed. This contrasts with his earlier correspondence which informed us that there were no trial protocols because "*the interventions belonged to our clinical practice*". This raises the question of what the Institutional Review Board actually approved.
- j) The information Dr Monticone reports regarding randomisation processes is useful and may explain the equal groups observed in each trial. This was present neither in the published trials nor in Dr Monticone's earlier responses to our queries.

- k) We are pleased to see incorrect data retracted from the literature. In earlier correspondence with Dr Monticone where we raised these anomalies, he expressed surprise at the duplication but indicated that he had checked the data and that they were what the staff had collected.
- l) In the examples of impossible p values that we raised in our paper, the means and standard deviations across the treatment groups were either identical or differed by one decimal place. On that basis, the reported p values cannot be correct.

Our investigation raised important concerns regarding the trustworthiness of these trials. The points raised in Dr Monticone's letter, and in his responses to our prior correspondence, do not adequately address those concerns, nor satisfactorily explain the extremely divergent results in this group of trials. At the time of writing, three of the studies had been withdrawn [3-5]; we have invited the editors of three remaining journals to consider retracting the five further studies which we judged untrustworthy.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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