Author’s response to reviews

Title: Improvement and decline of cognitive function in schizophrenia over one year: a longitudinal investigation using latent growth modelling.

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Author’s response to reviews:

Dear Dr Appleford,

Many thanks for your comments on our paper. We have revised relevant sections of the manuscript in response to the criticisms and constructive comments of the referees. We would like to resubmit it for your consideration for publication in BMC Psychiatry.

In answer to the individual reviewers’ comments:

Responses to review by Deborah Finkel
1. We accept the argument that, a priori, there is no reason to assume that trends in cognitive performance over time will be linear, and we aspire to characterise more complex patterns, in the cognitive profile(s) of our study participants. However there is little scope in our study, given the sample size and extent of missing data, to reliably estimate individual differences in curvilinear change. We remain convinced that a linear trend, varying between participants, is still a useful analytical approach to our research questions, and expect our results to be more generalisable from confining ourselves to this parsimonious model. Technical literature on simulation studies for power analyses in repeated measures designs could be marshalled to support our position but we do not want to overload the paper with methodological focus at this level of detail. We hope that our paper will appeal to two audiences, clinical psychiatrists and neuropsychologists, but hope also that methodologists will find our approach to the data both appropriate and fit for purpose, given the limitations we have already declared in our discussion (where these points were already raised).

2. We have undertaken the analyses suggested by the reviewer and have included the results in the manuscript (pages 10-12). We used logistic regression to consider whether demographic and clinical characteristics of patients predicted dropout (at any point). In addition, we assessed whether dropout at any one time-point could be predicted by cognitive performance at the previous assessment. In summary, there were no reliable demographic or clinical predictors of dropout, and no cognitive predictors of dropout at the second and third waves of assessment. However dropout at the final assessment was marginally predicted by performance on two cognitive tasks at the preceding assessment. Clearly these analyses are limited in power due to the small sample size. Nonetheless, they do provide more information about the validity of the missing at random assumption, which seems more valid than the Missing Completely At Random assumption of the complete case analyses, and suggests that our models will be less biased than this simple (delete any subject with missing data) approach.

3. It is our impression that practise effects cannot be measured in this study design because at any one assessment, all individuals have had the same number of previous assessments (i.e. the same amount of practise). We would be grateful for any suggestions as to how practise and timepoint could be dissociated within this design.

4. These effects were indeed modelled in the study; results are shown in Table 3.
5. The additional files supplied with the manuscript (as an excel spreadsheet) contain the residual variances asked for by the reviewer.

Responses to review by Terry Goldberg

1. The study reported is part of two randomised controlled trials of antipsychotic medication prescribed by clinicians in the UK (see pages 4 and 5), not a phase I or II trial.

2. Latent growth modelling and random effects models are different terms for the same models; we have clarified this point (p8).

3. We thank the reviewer for this important point and accept that the paper is something of a hybrid, containing points of both methodological and substantive interest. Whether cognitive function is stable or fluctuates over time in schizophrenia, and what affects this in the drug trial context, are clinically significant questions. The study is an opportunistic analysis of these questions in an important and unusual dataset. The data presented here offer insight into the cognitive correlates of the clinical changes detailed in the main CUtLASS trials. However due to the design of the trials, we cannot provide definitive answers about the effects of antipsychotic drugs on cognition. We are able however to demonstrate the feasibility of analysing such data using latent growth models, even when there is substantial missing data (as is the norm in psychiatric trials).

We hope that we have now answered all of the reviewers' concerns and that you will now be able to reconsider the manuscript for publication in BMC Psychiatry.

Yours sincerely,

Jennifer Barnett

On behalf of the authors.