Reviewer's report

Title: The Relationship, Structure and Profiles of Schizophrenia Measurements: A Post-hoc Analysis of the Baseline Measures from a Randomized Clinical Trial

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Reviewer: Sofia Brissos

Reviewer's report:

The authors present an interesting and important analysis on schizophrenia measurements used in clinical trials. They conclude that it is necessary to collect data on psychopathology, functioning/daily living and subjective well-being, although there seems to be some redundancy in some of the scales usually used, leading to a waste of time and useful resources and with no important gains. This has important implications in guiding future research, either clinical trials or other. Therefore, this manuscript is likely to be of importance for the scientific community.

However, the reviewer has some comments that could potentially improve the manuscript:

1. Background section:
   a. Please specify the study hypotheses.

2. Methods section:
   a. Patients were enrolled while in the acute phase. This means that their symptoms at the time may have influenced the other scales in a manner that might different when they are in a more stable phase of the disorder. In that sense, we think it would be more relevant to have performed the present analysis after discharge and/or in outpatients. However, the authors might be planning to do so, and in that case, it would be very interesting to see whether the results remain similar or not.
   b. Following the previous point, the fact that the study was undertaken in acute phase patients should be reflected in the title.
   c. The authors used a quality of life (QoL) scale that is administered by the clinician. Again, this raises the “old question” between objective and subjective indices of QoL. QoL can be adequately reported by outpatients or those in remission, but not so adequately by inpatients. Subjective or objective assessment seems to be different according to level of symptoms, and patients with active symptoms may not have the sufficient insight or functional capacity to perform a self-evaluation. Moreover, assessing QoL during admission probably only reflects a small time-point in that patient’s life, and for me it is more important to evaluate QoL while in the outpatient setting.

3. Discussion section:
a. The authors state that the findings suggest redundancy among the measures studied, particularly among the clinician-rated functional and quality of life measures:

i. We (Brissos et al, Schizophr Res 2011) and others have found no correlation between functioning and self-reported QoL in stabilized schizophrenia patients. Therefore, the present correlations could be due to several factors, namely the scales which were used (objective versus subjective ratings), and the fact that patients were in an acute state. Please make a brief comment on this, either on the discussion or limitations’ section.

ii. Clinician-rated instruments are sometimes rated by non-psychiatrists, and this could also have an influence on the results of clinical trials.

iii. The PANSS has been criticized by several authors, especially due to the necessary 30-points correction. Could the authors make a brief statement on whether psychopathological scales used in clinical trials should be re-formulated?

b. Cognitive function is rarely measured in clinical trials, and again, several batteries and/or brief tests have been proposed for this purpose (a recent article by our group has also focused on this subject: Brissos et al, Ann Gen Psychiatry, 2011). Could the authors make a brief comment on this?

c. Following the previous point, biomarkers have also been rarely used in clinical trials, and this could help in better capturing potential treatment outcomes and allow a richer characterization of the subgroups involved. The same is true for pharmacogenomics. Should these be included in future clinical trials?

d. Staging schizophrenia patients could also be important in clinical trials, since patients with long illness duration will probably have different responses, as compared to more chronic patients (which are the majority of patients included in clinical trials).

4. Conclusions:

a. The authors suggest that researchers should collect data across psychopathology, functioning/daily living and subjective well-being, but do not propose which scales are best to be used for this purpose. This should be added in the discussion section to better support the present conclusions.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

Yes. The reviewer is a full-time employee at Janssen-Cilag since April 2010, as
Medical Affairs Manager. Moreover, she has published some papers on functioning and cognition in schizophrenia patients, and therefore has her own “personal opinion” on these matters.