Author's response to reviews

Title: Treatment of bipolar disorder in the Netherlands and concordance with treatment guidelines. Study protocol of an observational, longitudinal study on naturalistic treatment of bipolar disorder in everyday clinical practice.

Authors:

Janwillem Renes (j.renes@altrecht.nl)
Eline J. Regeer (e.regeer@altrecht.nl)
Trijntje Y.G. van der Voort (n.vandervoort@ggzingeest.nl)
Willem A. Nolen (w.a.nolen@psy.umcg.nl)
Ralph W. Kupka (r.kupka@ggzingeest.nl)

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Author's response to reviews: see over
Dear mr. Carlo Rye Chua,

We like to thank the reviewers for their valuable comments. In this letter we will respond to the comments point-by-point, and point out which revisions have been made in the manuscript.

Referee 1:
The abstract is very long. It is preferred to be 250 words so it is not truncated in some search engines.
- We have shortened the abstract substantially to 243 words.

Page 4, paragraph 2.
There is a need for a sentence to explain why the authors review collaborative care.
- Like the reviewer already points out we review collaborative care programs because it shows there is already some evidence that following evidence based care produce better outcomes. Since the care described in the current Dutch guideline, published in 2008, resembles these collaborative care programs in many ways, concordance with this guideline may favor treatment outcome. We have added the following sentence at page 5, line 19: “Since the care recommended in the Dutch guideline for bipolar disorder resembles the previous mentioned specialty programs in many ways, concordance with the guideline is expected to improve quality of care and favor treatment outcome.”

Pages 4 and 5.
The 2nd paragraph of the background fills most of both page 4 and all of page 5. Please split this into three or more easier to follow paragraphs.
- We have split the text background in more paragraphs.

Page 6, lines 2-3
Does the Dutch guideline apply to bipolar I, bipolar II, bipolar NOS and schizoaffective disorder bipolar type.
- In the Dutch guideline it is stated that the guideline applies to patients with bipolar disorder. This includes bipolar I, II disorder and bipolar NOS. Schizoaffective disorder, bipolar type is included since in our view the guideline also applies to this disorder. There is currently no separate guideline for patients with schizoaffective disorder in the Netherlands. Psychiatrists will use recommendations from the guideline for bipolar disorder or the guideline for schizophrenia, or both, in patients with
schizoaffective disorder. We have added the following sentence at page 5, line 25: “Patients with these disorders are included in the study, since the Dutch guideline for bipolar disorder applies to these diagnostic categories.”

Page 6, line 11.
The question is what kind of sample it concerns, a consecutive sample, complete sample, random sample or convenience sample for each psychiatrist.

- It concerns complete samples in the sense that psychiatrists are asked to approach all their eligible patients. This will of course result in a random sample of patients willing to participate. Page 6, line 9 is changed to: “At baseline they are asked to invite all their eligible patients to participate in the study”.

Page 6, line 14. Why is the study completed at 2 time points? There is evidence that patients recall their mental state, treatment and contacts with health services up to 3-4 months but there is considerable doubt about accuracy of recall at 12 months. There are likely to be problems of low response rates among patients and high attrition rates. It would be good if all these issues were discussed. Might be better to get psychiatrists to complete all information as response rates would probably be higher.

- This is an important question raised by the reviewer. Although we acknowledge recall bias may be a problem, we chose a timeframe of 12 month since patients with a wide variety in the severity of bipolar disorder will be included. Patients who are doing well will have only a few contacts a year. This will mean they will not be able to report on care used with a shorter timeframe. Another reason why we chose a longer timeframe is the fact that we want to study whether adjustments in the care (resulting in more or in less concordance with guideline) will affect quality of care and treatment outcome. Since adjustments in care provided usually go slow, we considered 12 month a minimum for this purpose. It is stated on page 6, line 19, that we decided to ask patients on treatments they receive and not their psychiatrists as it can be expected that psychiatrists will be less able to report accurate on this than patients themselves. Moreover, if psychiatrists are asked to report on the care provided for the prospective part of the study, this might influence the care they provide. We would not be able then to measure concordance with the guideline in a non-biased setting. To clarify some of these issues we have added the following sentence to the text on page 6, line 13: “Although 12 months follow-up may seem long and may cause some recall bias, 12-months follow-up is chosen because patients who are doing well may receive no care within a shorter duration of follow-up. And since one of the aims of the study is to investigate whether improvement in concordance with the guideline over time may lead to better quality of care and treatment outcome, enough time between measurements is needed to make changes in the care provided possible.” And the following line was added at page 6, last line: “Also when this information is provide by health care providers it may influence the care they provide, and subsequently influence concordance with the guideline.”

Page 6, last line. “Exploratory” usually used instead of “explorative”. Good
practice to do this pilot so a strength of the design. Low response rate of psychiatrists was somewhat disappointing. Do you know what proportion of these psychiatrists saw patients with bipolar disorder? Response rate might be quite high among those that do.

- "Explorative" is replaced by "exploratory" as suggested by the reviewer on page 7, line 9. We do not have any information on the psychiatrists that did not respond at all. However the findings of our first survey show that the more patients with bipolar disorder psychiatrists treat, the more likely they are to be willing to participate in further research, as one might expect. Of the responding psychiatrists that only treat less than 10 patients with bipolar disorder, 66.0% was not interested in participating in further research, while this was only 17.4% in psychiatrist treating over more than 40 patients with bipolar disorder.

Page 7 line 21.

- "part" is replaced by "proportion" as suggested by the reviewer on page 8, line 5.

Page 8. Should discuss the psychometric problems of converting interview measures to self-rated measures. Is there any psychometric data on the self-report measures?

- Only the CGI-BP and the FAST have been used as self-rated instruments instead of rating by a clinician. There are until now no psychometric data available for either the CGI-BP or FAST used in this way. We will provide data on the FAST comparing self-rating scores with interview ratings, since this will be part of the current project. The following was added to the text, page 8, line 17: “Although the original clinician-rated CGI-BP-change has been validated [17], there are no data available on a self-rating version that we are aware of. A problem with a self-rating version may be that patients may overestimate or underestimate symptoms and functioning in comparison with a clinician rating.” and page 9 line 8: “There is discussion on patients’ ability to score quality of life or functioning on self-rating scales as it may be biased by mood state. However within this study it was not possible to implement clinicians rating scales.”

Page 11. Statistical analysis section is a bit weak. Data will be clustered so there are problems of merely aggregating data (one service may provide interventions such as group psychoeducation to the patients of several psychiatrists, while several patients may be entered from each psychiatrist).

- Interventions that patients receive will not be analysed in relation to individual psychiatrists. Only organisation of care and the relationship with concordance with the treatment guideline will be assessed.

Page 12, line 18.

- "Chance" is replaced by "change".

Referee 2:
The reviewer requested the term study protocol could be included in the title.

- We have included study protocol in the title.

Overall readability, but particularly more use of paragraphs on page 8,9 and 11-12.
Referee 3:
Concerning comment 1.) In my opinion, it may be difficult to achieve the desired outcome because only a quarter of the psychiatrists contacted (24.4%) agreed to take part in this survey. If one assumes that the distribution of bipolar patients is nearly equal over all contacted psychiatrists and that only every second patient agrees to participate in the study (which is very optimistic) - the authors will include a maximum of 10% of the bipolar population in the Netherlands. This seems far from representative. The authors are encouraged to seek other ways of recruiting the bipolar patients.

- We like to thank the reviewer to raise the important issue of generalisability of study results when only a smaller proportion of psychiatrists are participating. When designing the study protocol the best way to recruit psychiatrists and patients has been thoroughly discussed. Since the study aims to investigate psychiatric outpatient treatment as usual one requirement to be met is that patients are actually in treatment. To ensure that we only would include patients with bipolar disorder who are in treatment at a psychiatric service, we decided to recruit patients through treating psychiatrists. Moreover by recruiting patients as well as their psychiatrists it also becomes possible to include questions about organisation of care in the study. We consider this an innovative part of the study. To avoid selection bias at the start of the study, we decided to approach all psychiatrists that are member of the Dutch Psychiatric Association. We are aware of a possible selection bias of psychiatrists who are willing to participate in the study. Especially psychiatrists working in speciality clinics or research settings may be more likely to participate, or as mentioned before, psychiatrists treating many patients with bipolar disorder may show more interest to participate in research on the treatment of this disorder. The question is then whether or not a selection bias of patients included in the study will occur. We anticipate on this possibility of selective recruitment by preparing a study that will compare the cohort in the current study with other research cohorts of bipolar patients in the Netherlands (including patients from a population study, a naturalistic treatment study, and several pharmacotherapy trials) as well basic data from patients of three large outpatient clinics for the treatment of bipolar disorder. That study will provide more insight in the generalisability of our results.

Concerning comment 2.) First survey among psychiatrist was held between Dec 09 and Feb 10 - why not give a reasonable timeline for the whole study in the ms? Which parts of the study are ongoing, which completed? Are changes in the study protocol possible?

- Since the study is well underway, changes in the protocol are no longer possible. We still submit the current manuscript with the methodology of the study since more researchers may currently design comparable studies. We hope to contribute to discussions concerning the design of these naturalistic studies and guideline implementation, which is a relatively new field in psychiatry. The study will last until mid 2014. To the manuscript the following is added to page 7, line 18: “The study is planned to end mid 2014.”
Concerning comment 3.) Authors are encouraged to point out in the ms what, apart from collecting huge amounts of data, the innovative character of the study is. Furthermore, what is the importance for the readers of BMC Psychiatry?

- In response to this comment, the following was added to the discussion section at page 13, line 14: “We think the design of the study is innovative since it combines information on everyday clinical practice, the impact of concordance with the guideline and the organization of care. Moreover concordance with the guideline will be assessed in different subgroups of patients requiring different treatment modalities as recommended in the guideline, instead of more general recommendations. We hope that with the publication of the methodology of our study, we will contribute to discussion on how studies on naturalistic treatments and concordance of treatment guidelines can be designed, helping to close the cap between evidence based treatments in guidelines and care in every day clinical practice.”

Comment 4.) What will be the consequences if the study shows that concordance of treatment with treatment guidelines is high or low? Will authors consider national guidelines as superfluous? (In my opinion the guidelines in the Netherlands are quit reasonable, especially the scheme for introducing mood stabilizers). Are lots of different national guidelines useful at all? Instead of investigating concordance with guidelines it might be better to investigate how to improve compliance/adherence to these guidelines, why not use techniques like Motivational Interviewing (this is because I speculate that concordance is quite low)?

- Since this is the first study of its kind in the Netherlands, we do not know whether concordance will be low. One could expect that certain treatments modalities recommended in the guideline are better implemented in daily clinical practice then others. Such findings will help further studies on implementation of guidelines. We also expect that in certain subgroups of patients will receive care more in concordance with the guideline then in other subgroups. This may help to identify caps in current treatment guidelines and improve guideline-development and implementation in the future. For these reasons we decided to perform the current study, which may be followed by more detailed studies on implementation. In the Netherlands one guideline for patients with bipolar disorder exists, and it is in line with international guidelines.

Concerning the question to include more information on the ethical approval of the study we can inform you that the Medical Ethical Committee of the University Medical Center Utrecht reviewed the study protocol and stated that no further requirements were necessary concerning the Dutch Medical Research in Human Subjects Act, as this is an observational, non-interventional study. In the Netherlands this approval by a Medical Ethic Committee is sufficient for a nationwide study, i.e., it was not necessary to obtain approval from all psychiatric institutions from which psychiatrists participated since the study does not interfere with treatment. In addition to the approval by the Medical Ethical Committee of the University Medical Center Utrecht the scientific committees of the two initiating centers, Altrecht Institute for Mental Health Care and GGZ inGeest/VU University Medical Center, independently reviewed the protocol for its
scientific content. We have moved this section in the manuscript to the method section and rewrote the text, page 6, as follows:

- "The study protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht, The Netherlands, and was in addition independently reviewed by the scientific committees of the main research centers, Altrecht Institute for Mental Health Care, Utrecht, The Netherlands, and GGZ inGeest/VU University Medical Center, Amsterdam, The Netherlands. All participating patients gave informed consent. Data are stored in a research database in accordance with the Dutch Data Protection Authority."

We thank you very much for your attention to our revised paper.

With kind regards, also on behalf of all authors,

Yours sincerely,

Janwillem Renes, MD

j.renes@altrecht.nl