

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	SCREENING FOR THE METABOLIC SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION: FINDINGS OF A SIX-YEAR QUALITY IMPROVEMENT PROGRAMME IN THE UK
<b>AUTHORS</b>	Barnes, Thomas; Bhatti, Sumera; Adroer, Roman; Paton, Carol

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Mark E. Schneiderhan University of Minnesota College of Pharmacy
<b>REVIEW RETURNED</b>	15-Feb-2015

<b>GENERAL COMMENTS</b>	<p>The information presented by Drs. Barnes, et al. is very relevant in emphasizing the need for more vigilant monitoring of metabolic syndrome, especially from primary care, in patients treated with antipsychotic agents. The following comments are to better understand the focus, research methodology, results, and conclusions described in the manuscript.</p> <ol style="list-style-type: none"><li>1. (Is the research question or study objective clearly defined? and Is the abstract accurate, balanced and complete?) There are minor variations in how the objectives are stated in the abstract and the manuscript. On page 2 of 15 (line 8 and 9), the abstract described the objective: "To increase the frequency and quality of screening for the metabolic syndrome in people prescribed continuing antipsychotic medication." In the manuscript the objective statement on page 3 of 15 (line 50 – 53) seems more vague by referring to the quality improvement program targeted at screening for metabolic syndrome. Recommend that the objectives be clear and consistent in the abstract and manuscript.</li><li>2. (Is the study design appropriate to answer the research question? and Are the methods described sufficiently to allow the study to be repeated?) The manuscript does not describe the randomization process and how subjects were identified. In a previous publication (Acta Psychiatr Scand 2008; 118: 26–33), it was clear that the Trusts were instructed to provide data from 'all subjects' taking antipsychotics to safe guard against selection bias. However, in the current manuscript (page 4 of 15 line 6-7) the Trusts were required to provide data on a "randomly-selected sample of eligible patients". Please explain how subjects were randomized by the Trusts.</li><li>3. (Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?) No evidence that a human subject institutional review board approved the study. The author needs to provide this information in the methods section.</li></ol>
-------------------------	--

	<p>4. (If statistics are used are they appropriate and described fully?) a) Please include the apriori sample size calculation for the audit. b) Please clarify how the baseline and subsequent re-audits were analyzed and compared to 2012 data. The statistical analyses (page 5 of 15; lines 4 – 18) appear to focus only on binary logistic regression results from the past year (2012). It is unclear about the statistical analyses performed on the baseline (2006) or prior re-audits. Since, the assumed objective of the manuscript was to determine the changes in frequency and quality of metabolic syndrome monitoring; recommend reporting odds ratios (95% confident intervals) to measure changes in outcome between audit periods?</p> <p>5. (Are the study limitations discussed adequately?) The discussion on page 8 of 15 lines 3-13 does not clearly explain there were no selection/reporting bias in the current study based on the generalizability of the large sample size and previous logistic regression analyses in the 2008 publication.</p> <p>a) Determine if there was any reporting bias, since the number of participating Trusts in 2012 increased (See table 1 on page 4 of 15); but the number of patients in the sample was 50% of what was reported in 2010 and less than what was reported in 2006. Recommend that additional statistical analyses (similar to the results reported in Table 3 on page 30 of the 2008 publication) to control for the variability in proportion of patients and number of Trusts participating at each re-audit.</p> <p>b) Is the decreased number of patients in the 2012 sample an indication of reduction in the overall population being monitored?</p> <p>c) Do the gender differences (M&gt;F) consistent in the current and previous audits reflect the prescribing practice for white women vs. white men or is this a confounding factor due to the randomization methods or selection process for screening used?</p> <p>The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.</p>
--	---

<b>REVIEWER</b>	Purushottam B. Thapa University of Arkansas for Medical Sciences Department of Psychiatry Little Rock, Arkansas United States
<b>REVIEW RETURNED</b>	09-May-2015

<b>GENERAL COMMENTS</b>	<p>The authors describe the impact of a quality improvement initiative through annual audits of participating mental health Trusts on monitoring for the metabolic syndrome in individuals who are prescribed antipsychotic medications. The risk of the metabolic syndrome in individuals with serious mental illness is of great concern. The authors are to be commended for reporting on the impact of a program to improve screening for these high risk individuals. The manuscript is well written. The authors appropriately acknowledge that the improvement in screening cannot be entirely explained by their program alone.</p> <p>Some recommendations to the authors:</p>
-------------------------	---

	<p>Abstract: The stated objective does not appear to be quite specific. While the general goal is to increase frequency of monitoring, this reviewer's understanding of this study is "to evaluate the impact of a QIP program via annual audits on the frequency of screening...."</p> <p>Methods: The authors state that this is a national sample but do not clarify how. For example, how many trusts and other programs were invited to participate and what percent participated. It is clear that the number of participating Trusts varied over the years, but did most of them participate every year? Trusts were asked to randomly sample patients; what percent of their patient populations were sampled. The authors assume that the samples were truly random.</p> <p>Analysis: The authors may want to test the significance of the trends in screening during the audit years -for example, a chisquare test for trends</p> <p>Tables and Figures:</p> <p>Figure 3 is basically a duplicating data in Table 1. Would recommend dtopping the figure and clarifying the text on Table 1</p> <p>Table 2 can be briefly described in the text and omitted. Recommned listing actual diagnoses with the codes in parentheses.</p> <p>Table 3. Simplify by removing reference category since it is the same for all three variables. Include a footnote stating that the dependent variable was "documentation of all four screening variables" categorized as "yes" vs "no" and the latter was the reference.</p> <p>Figure 1 could be laid out in one template as opposed to 4.</p>
--	--

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Mark E. Schneiderhan  
Institution and Country University of Minnesota

Please leave your comments for the authors below.

The information presented by Drs. Barnes, et al. is very relevant in emphasizing the need for more vigilant monitoring of metabolic syndrome, especially from primary care, in patients treated with antipsychotic agents.

Response: Thank you for this positive comment on the paper.

The following comments are to better understand the focus, research methodology, results, and conclusions described in the manuscript.

1. (Is the research question or study objective clearly defined? and is the abstract accurate, balanced and complete?) There are minor variations in how the objectives are stated in the abstract and the manuscript. On page 2 of 15 (line 8 and 9), the abstract described the objective: “To increase the frequency and quality of screening for the metabolic syndrome in people prescribed continuing antipsychotic medication.” In the manuscript the objective statement on page 3 of 15 (line 50 – 53) seems more vague by referring to the quality improvement program targeted at screening for metabolic syndrome. Recommend that the objectives be clear and consistent in the abstract and manuscript.

Response: The aim of the audit-based quality improvement programme was indeed to ‘increase the frequency and quality of screening for the metabolic syndrome in people prescribed continuing antipsychotic medication’ by feeding back to clinicians their benchmarked performance data against evidence-based practice standards for such screening and prompting reflective practice and action plans to tackle areas where they fell short of the standards (as well as providing change interventions to support such action plans). We have amended the text to make this clearer.

2. (Is the study design appropriate to answer the research question? and are the methods described sufficiently to allow the study to be repeated?) The manuscript does not describe the randomization process and how subjects were identified. In a previous publication (*Acta Psychiatr Scand* 2008; 118: 26–33), it was clear that the Trusts were instructed to provide data from ‘all subjects’ taking antipsychotics to safe guard against selection bias. However, in the current manuscript (page 4 of 15 line 6-7) the Trusts were required to provide data on a “randomly-selected sample of eligible patients”. Please explain how subjects were randomized by the Trusts.

Response: As the reviewer points out, each participating clinical team was asked to review the clinical records of every patient on their case load who was prescribed antipsychotic drugs at the time of the audit, and the text has been amended to reflect that. In most of our other quality improvement programmes we have asked Trusts to provide ‘randomly-selected sample of eligible patients’ and this phrase was included in the paper in error.

3. (Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?) No evidence that a human subject institutional review board approved the study. The author needs to provide this information in the methods section.

Response: This was an audit-based, quality improvement programme not a research study and no ethical approval was required.

4. (If statistics are used are they appropriate and described fully?) a) Please include the a priori sample size calculation for the audit. b) Please clarify how the baseline and subsequent re-audits were analyzed and compared to 2012 data. The statistical analyses (page 5 of 15; lines 4 – 18) appear to focus only on binary logistic regression results from the past year (2012). It is unclear about the statistical analyses performed on the baseline (2006) or prior re-audits. Since, the assumed objective of the manuscript was to determine the changes in frequency and quality of metabolic syndrome monitoring; recommend reporting odds ratios (95% confident intervals) to measure changes in outcome between audit periods?

Response: As this was an audit-based quality improvement programme rather than a research study, no sample size calculation was performed. Regarding the comments on statistical analysis, please see also response to comment 5 below.

5. (Are the study limitations discussed adequately?) The discussion on page 8 of 15 lines 3-13 does not clearly explain there were no selection/reporting bias in the current study based on the

generalizability of the large sample size and previous logistic regression analyses in the 2008 publication.

a) Determine if there was any reporting bias, since the number of participating Trusts in 2012 increased (See table 1 on page 4 of 15); but the number of patients in the sample was 50% of what was reported in 2010 and less than what was reported in 2006. Recommend that additional statistical analyses (similar to the results reported in Table 3 on page 30 of the 2008 publication) to control for the variability in proportion of patients and number of Trusts participating at each re-audit.

Response: We have heeded these comments and conducted a multilevel logistic regression analysis of the trend in metabolic syndrome screening data across the six audits, which also took account of variations in participating Trusts over time. This analysis is described in the 'statistical analysis' section, the results are provided in the 'Results' section in the form of odds ratios, indicating the relative change in the odds of an outcome related to screening for the metabolic syndrome occurring over the years of the programme. Our interpretation of the findings has been added to the 'Discussion' section.

b) Is the decreased number of patients in the 2012 sample an indication of reduction in the overall population being monitored?

Response: It reflects fewer assertive outreach teams participating on that occasion.

c) Do the gender differences (M>F) consistent in the current and previous audits reflect the prescribing practice for white women vs. white men or is this a confounding factor due to the randomization methods or selection process for screening used?

Response: No, this probably reflects the gender profile of patients under the care of assertive outreach clinical teams.

Reviewer: 2

Reviewer Name Purushottam B. Thapa, M.D., M.P.H.  
Institution and Country University of Arkansas for Medical Sciences

Please leave your comments for the authors below The authors describe the impact of a quality improvement initiative through annual audits of participating mental health Trusts on monitoring for the metabolic syndrome in individuals who are prescribed antipsychotic medications. The risk of the metabolic syndrome in individuals with serious mental illness is of great concern. The authors are to be commended for reporting on the impact of a program to improve screening for these high risk individuals. The manuscript is well written. The authors appropriately acknowledge that the improvement in screening cannot be entirely explained by their program alone.

Response: Thank you for your positive comments on the paper.

Some recommendations to the authors:

Abstract: The stated objective does not appear to be quite specific. While the general goal is to increase frequency of monitoring, this reviewer's understanding of this study is "to evaluate the impact of a QIP program via annual audits on the frequency of screening...."

Response: The aim of the audit-based quality improvement programme was to increase the frequency and quality of screening for the metabolic syndrome in people prescribed continuing

antipsychotic medication by feeding back to clinicians their benchmarked performance data against evidence-based practice standards for such screening and prompting reflective practice and action plans to tackle areas where they fell short of the standards (as well as providing change interventions to support such action plans). We have amended the text to make this clearer. In terms of evaluation, please see our response below regarding additional statistical analysis.

#### Methods:

The authors state that this is a national sample but do not clarify how. For example, how many trusts and other programs were invited to participate and what percent participated. It is clear that the number of participating Trusts varied over the years, but did most of them participate every year? Trusts were asked to randomly sample patients; what percent of their patient populations were sampled. The authors assume that the samples were truly random.

Response: Each participating clinical team was asked to review the clinical records of every patient on their case load who was prescribed antipsychotic drugs at the time of the audit, and the text has been amended to reflect that. In most of our other quality improvement programmes we have asked Trusts to provide 'randomly-selected sample of eligible patients' and this phrase was included in the paper in error.

Analysis: The authors may want to test the significance of the trends in screening during the audit years -for example, a chi-square test for trends

Response: We have conducted a multilevel logistic regression analysis of the trend in metabolic syndrome screening data across the six audits, which also took account of variations in participating Trusts over time. This analysis is described in the 'statistical analysis' section, the results are provided in the 'Results' section in the form of odds ratios, indicating the relative change in the odds of an outcome related to screening for the metabolic syndrome occurring over the years of the programme. A summary of the findings has been added to the 'Discussion' section.

#### Tables and Figures:

Figure 3 is basically a duplicating data in Table 1. Would recommend dropping the figure and clarifying the text on Table 1

Response: Given the overlap in data between Table 1 and Figure 3, we have deleted the latter (and amended the text appropriately) and added the number of participating clinical teams at each audit to the former.

Table 2 can be briefly described in the text and omitted. Recommend listing actual diagnoses with the codes in parentheses.

Results: Presenting the data in Table 2 as text would be rather wordy. We have kept Table 2 and added 'actual diagnoses', as suggested.

Table 3. Simplify by removing reference category since it is the same for all three variables. Include a footnote stating that the dependent variable was "documentation of all four screening variables" categorized as "yes" vs "no" and the latter was the reference.

Response: Thank you for the suggestion, but we consider the Table is clearer as currently presented.

Figure 1 could be laid out in one template as opposed to 4.

Response: Thank you for the suggestion, but we consider that the Figure is clearer as it currently appears (having previously tried other ways of presenting these data).

#### VERSION 2 - REVIEW

<b>REVIEWER</b>	Purushottam B. Thapa University of Arkansas for Medical Sciences USA
<b>REVIEW RETURNED</b>	26-Jul-2015
<b>GENERAL COMMENTS</b>	The authors are to be commended for addressing the questions raised by the reviewers.