PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Development and validation of an instrument for measuring the burden of medicine on functioning and well-being: the Medication-Related Burden Quality of Life (MRB-QoL) tool
AUTHORS	Mohammed, Mohammed; Moles, Rebekah; Hilmer, Sarah; Kouladjian O'Donnell, Lisa; Chen, Timothy

VERSION 1 – REVIEW

REVIEWER	Rhiannon Braund University of Otago, New Zealand
REVIEW RETURNED	21-Aug-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. It is timely and indeed there is the need for this type of tool in the area evaluating pharmaceutical care and other related areas. While this paper has many minor finishing/formatting errors such as extra spaces, inconsistent reference formatting, missing full stops (ie) and the occasional typo ("pooper" instead of "poorer") the language and readibility of this paper is good. My concerns are mainly minor however, I think that the authors should consider the implications. One concern is the use of a research company and an electronic survey to deliver the tool. While I understand why this was chosen, it does limit the population to those patients that are computer savvy. Also I would expect that in this tool would be used in a patient care setting, so the population may be slightly different. Upon reading the abstract I was unclear on the "functional and role limitation" category. This became clearer upon reading the full paper, but I wonder if there might be another phrase that adequately describes this category. Maybe impact on function. I would add under the strengths of this study that this tool fills a need in pharmacotherapy research. Minor typos: Page 5 line 32. i.e. Page 5, line 34. Query the need for ";" after Thus Page 5, line 48. Should "drug" be replaced with "medicine"? Page 8, line 39. Should "hassles" be replaced with "inconvenience"? Page 9, line 52. ie Page 10, line 10. "pooper" :) Page 11, line 54. Consistency in capitalisation of "Functional and Role Limitation" Page 12, line 30. Number of medicine"s" Page 14, line 8. Consistency of capitalisation "Functional and Role Limitation"

REVIEWER	Sirois, Caroline Professor, Department of Social and Preventive Medicine, Laval University, Canada Professor, Faculty of Medicine, Limoges University, France CS acknowledges that one of the authors is co-investigator on a research grant proposal submitted for funding. Other reviewers have no conflict of interests to declare.
REVIEW RETURNED	30-Aug-2017

GENERAL COMMENTS	The authors describe how they developed and validated an instrument designed to measure medication-related burden on functioning and well-being. The article is interesting and well presented. The authors clearly describe the genuine need to develop and use such a medication related quality-of-life questionnaire. We believe this kind of questionnaire is of great interest. It could notably be used in clinical trials, because benefits and risks alone often do not clearly indicate what impact medications have on patients' quality of life. Furthermore, patients often perceive risks and benefits differently from clinicians, which could affect the perceived burden of medication. It is therefore paramount to evaluate patients' perceptions. The authors performed a comprehensive literature review. The development of the tool is rigorous and thorough. We did not identify any major issues with the document. However, we felt the article would gain from shortening its length. We have also some minor comments detailed below. MINOR ISSUES 1. Page 5, line 25. Many readers are not familiar with pharmaceutical care. We believe it would be helpful to provide more details on what this concept entails. (On the same page, a suggestion on line 30: Instead of writing adding "the core elements," the sentence could simply read: "However, it is not known how identification and resolution of drug-related problems…"; it would be easier to understand what exactly is linked to outcomes.) 2. Page 7, figure 1: Would it be possible to move Phase IA up? We felt it would be easier to read from top to bottom. Also, in the "Generation of item bank" square, an item seems to be missing following "Authors'". 3. Page 8, Item pool. Quotes: It would be interesting if the authors provided more details on the basis of their work with selecting quotes. Is there any methodological work supporting this approach? (It seems to be so, as the authors cite a reference in the discussion section.) Were there any inclusion criteria for the quotes chosen? It would be interesting that the authors discuss this method in the discussion section: Are there any variables and settings that could affect the results? For example, do we expect changes with calendar years (as the perceived risk of medications, for example, tend to change with years)? Would the themes be different according to specific diseases or countries? 4. Page 8, Study sample and data collection: We felt that the

	Internet survey generated some limitations. For example, we were uncertain that older participants, who are less familiar with the Internet would be as prone as younger ones to participate. It would be important to give more details on how the participants were contacted. Were they paid or did they get any compensation, as they were recruited by a marketing company? Was it a random selection among those individuals responding to the inclusion criteria? How exactly were they recruited? The authors could discuss how potential selection bias could affect their results (wouldn't the study design exclude those individuals more at risk of experiencing the strongest impact of medications on quality of life, i.e. older individuals with more medicines who may not be able to complete the survey?) How many individuals did not complete the survey? 5. Page 10, Data analysis: How were OTC drugs and natural products managed in the analysis? Was there enough information to include them in the DBI or MRCI calculation, for example? 6. Page 10, Data analysis, line 10: Since there is no universal definition of multimorbidity, it would be interesting to know why the presence of 3 conditions was chosen as a threshold for multimorbidity. Could the authors mention a reference for this choice? 7. Results, page 11. In order to fully appreciate the results, it would be interesting if the authors provided more details: 1- Please describe the scale of the questionnaire (results could span from what to what?) ; 2- Is there a total score, or is the scale used factor by factor? 3- How should clinicians use the scale in clinics? Is there a threshold that should trigger an "alarm" in clinics? 8. Table 1. Some elements should be included in the Table to ensure it can stand autonomously. The number of individuals should be added in the title. For each variable, please identify that the number reported is a median (as it is stated in the variable age). 9. Page 15, line 49. "Due to higher levels…" this sentence belongs more in the discussion section than results. 10. Table 4. Level of statistical significance (alpha value) should be provided with the table. (i.e. A P value <0.05 was considered statistically significant.) TYPOGRAPHIC ELEMENTS 11. Page 4, Strengths and Limitations of this study, line 17: "test-retest" instead of "test-rest" 12. Page 5, line 34, Unnecessary semicolon after "thus" 13. On two occasions (lines 10, page 10 and page 15, line 51), "poorer" seems to be misspelled "pooper". 14. Page 16, Table 5: IQR are reported without decimals except for two results: (<3 conditions and <3 number of medicines); to ensure consistency, we suggest presenting them without decimals. 15. Page 21, line 41. However needs a cap H. 16. Page 24, References: Some journal titles are abbreviated and some not.

VERSION 1 – AUTHOR RESPONSE

Reviewer1: Rhiannon Braund

General comment: Thank you for the opportunity to review this manuscript. It is timely and indeed there is the need for this type of tool in the area evaluating pharmaceutical care and other related areas. While this paper has many minor finishing/formatting errors such as extra spaces, inconsistent reference formatting, missing full stops (ie) and the occasional typo ("pooper" instead of "poorer") the language and readability of this paper is good.

Comment 1
My concerns are mainly minor however, I think that the authors should consider the implications. One concern is the use of a research company and an electronic survey to deliver the tool. While I understand why this was chosen, it does limit the population to those patients that are computer savvy. Also I would expect that in this tool would be used in a patient care setting, so the population may be slightly different.

Response: Thank you for pointing out this important point. Development of our measure was informed by a rigorous approach. The item generation was based on data from 34 qualitative studies involving 1144 participants, conducted across different health care settings in 12 countries. However, the validation stage was informed by a survey from community dwelling adults living with chronic medical conditions and taking multiple medicines. We agree with the reviewer that our sample may differ from other populations and was restricted to those who were computer literate. However, we believe that the difference will only be in terms of intensity of the burden rather than type of the burden being encountered. For example, hospitalized patients or patients in nursing homes may have a higher level of burden due to multiple comorbidities and complexity of the medication regimen. In our study, the lower level of burden observed in most domains of MRB-QoL indicated that our study participants were relatively well-functioning and, possibly on less complex medication regimens. Using MRB-QoL measure in more diverse settings, including patient care settings, and with individuals with low computer literacy will be considered in future research and further psychometric validation of the tool. We have elaborated on the drawbacks of using an on-line survey and consumer panel for this research. This issue has now been discussed in the revised manuscript.
See page 21-22 “A possible limitation of an on-line survey is only participants who were computer literate and who had access to the internet could participate. It is noteworthy, however, that our study sample did include older people taking multiple medicines. One hundred seventy-six participants were aged ≥65 years and the median number of prescription medicines taken was 5 (3-7). Furthermore, the potential sampling bias, of having only computer literate participants with access to the internet, is unlikely to affect the results of psychometric testing (i.e. the factor structure). However, the extent of burden observed in the scores of MRB-QoL sub-scales and relatively low complexity of medication regimen observed in the MRCI, may reflect that participants were well functioning community dwelling adults. Intensity of the burden in the MRB-QoL, DBI and MRCI may have been different if participants were recruited from hospitals, nursing homes or patients with more complex medicine regimens.”

Comment 2

Upon reading the abstract I was unclear on the "functional and role limitation" category. This became clearer upon reading the full paper, but I wonder if there might be another phrase that adequately describes this category. May be impact on function.
I would add under the strengths of this study that this tool fills a need in pharmacotherapy research.

Response:
Thank you for the comment: An additional explanation has been added to the abstract.
See Page 4 line 6-8: “This tool fills a need in pharmacotherapy research and has also a potential for use as a screening tool in clinical practice to identify patients at high risk of experiencing medication related burden.”

Minor typos
Thank you for pointing out these errors. All typographical errors have been corrected in the revised manuscript.

Comment 3
Page 5 line 32. i.e.

Response: Thank you. Comment accepted.
See page 5 “It is not known how the core elements of PC interventions (i.e. identification and resolution of drug related problems) is linked to changes in humanistic outcomes.”

Comment 4
Page 5, line 34. Query the need for ";" after Thus

Response: Comment accepted and correction has been made in the revised manuscript.
See Page 5 “Thus, demonstrating the full picture of the benefit of PC services in improving patients’ HRQoL outcomes remains challenging.”

Comment 5
Page 5, line 48. Should "drug" be replaced with "medicine"?

Response: Comment accepted and the word “drug” has now been replaced with “pharmacotherapy” in the revised manuscript.
See page 5 “These measures, however, have been developed to evaluate the impact of disease burden on patients’ life not specifically the impact of pharmacotherapy.”

Comment 6
Page 8, line 39. Should "hassles" be replaced with "inconvenience"?

Response: Comment accepted and the word “hassles” has now been replaced with “inconvenience” in the revised manuscript.
See page 8 “In light of this, items of MRB-QoL were designed in a way to typically focus on medication burden ranging from the inconvenience of dealing with routines to the burden on social, psychological, physical and financial well-being.”

Comment 7
Page 9, line 52. ie

Response: Comment accepted.
See page 9 “Testing convergent (moderate to high correlations i.e. r >0.3)33 discriminant (weak correlations i.e. r ≤ 0.3) validity of MRB-QoL.”

Comment 8
Page 10, line 10. "pooper" :)

Response: The word “pooper” has now been replaced with “poorer” in the revised manuscript.
See page 10 “…DBI>0 may have poorer MRB-QoL, we planned to test known group validity of the MRB-QoL…”

Comment 9
Page 11, line 54. Consistency in capitalization of "Functional and Role Limitation"

Response: Comment accepted.
See page 11 ‘‘Factor 3: “Functional and Role Limitation” (items 18-24)”

Comment 10
Page 12, line 30. Number of medicine"s"

Response: Comment accepted.
See page 12 “Number of medicines (PsyB-2)”

Comment 11
Page 14, line 8. Consistency of capitalization "Functional and Role Limitation"

Response: Comment accepted.
See page 14 “Moderate correlation between DBI and the “Functional and Role Limitation” sub-scale of MRB-QoL provided some evidence…”

Reviewer: 2
General comments
The article is interesting and well presented. The authors clearly describe the genuine need to develop and use such a medication related quality-of-life questionnaire. We believe this kind of questionnaire is of great interest. It could notably be used in clinical trials, because benefits and risks alone often do not clearly indicate what impact medications have on patients’ quality of life. Furthermore, patients often perceive risks and benefits differently from clinicians, which could affect the perceived burden of medication. It is therefore paramount to evaluate patients’ perceptions.
The authors performed a comprehensive literature review. The development of the tool is rigorous and thorough. We did not identify any major issues with the document. However, we felt the article would gain from shortening its length. We have also some minor comments detailed below

Response
Thank you for the comment. The discussion section of our manuscript has now been shortened. It is now more compact and focused on our pertinent findings.

MINOR ISSUES
Comment 1

Page 5, line 25. Many readers are not familiar with pharmaceutical care. We believe it would be helpful to provide more details on what this concept entails. (On the same page, a suggestion on line 30: Instead of writing adding “the core elements,” the sentence could simply read: “However, it is not known how identification and resolution of drug-related problems…"; it would be easier to understand what exactly is linked to outcomes.)

Response: Thank you for this important point. A brief explanation of the concept of pharmaceutical care has been provided in the revised manuscript.
See page 5 ‘‘…Pharmaceutical Care’ (PC) services 7 defined as “responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life.” It is medication therapy focused health care provided to achieve improved medication therapy and quality of life for patients.”

Comment 2
Page 7, figure 1: Would it be possible to move Phase IA up? We felt it would be easier to read from top to bottom. Also, in the “Generation of item bank” square, an item seems to be missing following “Authors’”.

Response:
Comment accepted and has now been incorporated in the revised manuscript.
See Page 7, Figure 1:

Comment 3
Page 8, Item pool. Quotes: It would be interesting if the authors provided more details on the basis of their work with selecting quotes. Is there any methodological work supporting this approach? (It seems to be so, as the authors cite a reference in the discussion section.) Were there any inclusion criteria for the quotes chosen? It would be interesting that the authors discuss this method in the discussion section: Are there any variables and settings that could affect the results? For example, do we expect changes with calendar years (as the perceived risk of medications, for example, tend to change with years)? Would the themes be different according to specific diseases or countries?

Response
Thank you for the comment. As has been stated on “page 8, methods section (item pool)” and “page 21, strengths and limitations”, the development process for the MRB-QoL was multi-dimensional. Specifically involved integration of the concepts of pharmaceutical care, HRQoL measures and medicine attributed burden, on health and well-being. This was informed by a series of three comprehensive systematic reviews. The basis for our pool of items was a systematic review with meta-synthesis of qualitative studies entitled “Medication Related Burden and Patients’ Lived Experience with medicine: a systematic review and meta-synthesis of qualitative studies” which comprehensively explored medication attributed burden on health and wellbeing, irrespective of the nature of medicine or medical condition. Over 966 participant quotes from original studies were included in this review and were used to generate an item bank. Some quotes were directly used whereas others were paraphrased to shorten the sentence or make it clearer. This approach to item development is similar to tool development based on qualitative interviews or focus group discussions, in that participant’s quotes are used to generate items. However, we believe this approach is more comprehensive in addressing a wide range of areas of interest (i.e. MRB) than commonly used methods (i.e. qualitative interviews or focus group discussions). Before selecting the quotes, we developed a conceptual model of MRB-QoL (attached as supplementary file 1) based on the three systematic reviews. Following the development of a conceptual model, all quotes were mapped to the domains within conceptual model.

Then all quotes within the domains of our conceptual model were evaluated and selected for an item bank. For each domain of the conceptual model, sample quotes were selected to develop a pool of 76 items of MRB-QoL.
The MRB-QoL is a generic measure of the burden of medicine on functioning and well-being. The meta-synthesis paper on which the generation of MRB-QoL items was based, revealed that there is a shared commonality of medication related burden regardless of the type of therapy and medical condition. Although we do not think that the domains of burden change over time, the intensity of the medication burden may vary from setting to setting. For example, due to the severity of the disease and complexity of medication regimen, hospitalized patients may have higher levels of medication burden than community dwelling well-functioning adults. Similarly, intensity of the burden may vary depending on the disease condition e.g. patients on cancer chemotherapy may have higher scores in "Functional and Role Limitation" domain than "Therapeutic Relationship" domain; patients on antiretroviral therapy for HIV or patients on antipsychotics may show higher scores on the "Social Burden" domain than other domains of MRB-QoL. Since validation of a tool is not a single step process, future research will look into MRB variation across health care settings, medical conditions or specific cohorts. However, we would like to bring to reviewer's attention that we have also received comments to shorten the length of the manuscript. Therefore, we felt that further discussion points may adversely affect the flow and coherence of the manuscript.

Comment 4
Page 8, Study sample and data collection: We felt that the Internet survey generated some limitations. For example, we were uncertain that older participants, who are less familiar with the Internet would be as prone as younger ones to participate. It would be important to give more details on how the participants were contacted. Were they paid or did they get any compensation, as they were recruited by a marketing company? Was it a random selection among those individuals responding to the inclusion criteria? How exactly were they recruited? The authors could discuss how potential selection bias could affect their results (wouldn't the study design exclude those individuals more at risk of experiencing the strongest impact of medications on quality of life, i.e. older individuals with more medicines who may not be able to complete the survey?) How many individuals did not complete the survey?

Response
Participants were recruited via a market research company based in Australia, the Survey Sampling Interview (SSI). Participants were invited to participate in this study via the SSI company. After setting up the MRB-QoL questionnaire on Survey Monkey, we sent the link to the survey to the recruiting company. The company facilitated screening of qualifying participants from their panel members and external invitations. They provided the link to our survey for participants who passed the screening criteria. In addition, we designed our own screening questions on SurveyMonkey so that individuals who did not meet the criteria for the study were automatically disqualified from taking part in the survey. Participants who did meet screening process of the recruiting company and our screening questions were then invited to complete the on-line MRB-QoL survey. The company, and study participants, received a financial incentive for their time.
We also share review's concern that one of the drawbacks of an on-line survey is that potential participants who are not able to use or access internet may be excluded. This issue has now been further discussed in the revised manuscript.
See page 21-22 "A possible limitation of an on-line survey is only participants who were computer literate and who had access to the internet could participate. It is noteworthy, however, that our study sample did include older people taking multiple medicines. One hundred seventy-six participants were aged ≥65 years and the median number of prescription medicines taken was 5 (3-7). Furthermore, the potential sampling bias, of having only computer literate participants with access to the internet, is unlikely to affect the results of psychometric testing (i.e. the factor structure).

However, the extent of burden observed in the scores of MRB-QoL sub-scales and relatively low complexity of medication regimen observed in the MRCI, may reflect that participants were well functioning community dwelling adults. Intensity of the burden in the MRB-QoL, DBI and MRCI may have been different if participants were recruited from hospitals, nursing homes or patients with more complex medicine regimens."

Comment 5
Page 10, Data analysis: How were OTC drugs and natural products managed in the analysis? Was there enough information to include them in the DBI or MRCI calculation, for example?

Response
Participants were asked to provide details (e.g. name, strength, dose, frequency of use) of the medicines they were taking including prescription, non-prescription (OTC) and complementary medicines (natural products). A sample medication regimen was provided to assist participants. The most commonly recorded non-prescription medicines were analgesic medicines and medicines for reflux. When relevant and when specific data were provided (e.g. name, strengths, dose, frequency), medicines were included in the calculation of DBI and MRCI. If information (i.e. name, strengths, dose, frequency) was incomplete, we excluded the drug from the analysis. OTC medicines were included in our analysis because the MRB-QoL aims to quantify patient level medication burden rather than prescription only medicine burden.

Comment 6
Page 10, Data analysis, line 10: Since there is no universal definition of multimorbidity, it would be interesting to know why the presence of 3 conditions was chosen as a threshold for multimorbidity. Could the authors mention a reference for this choice?

Response
Thank you for this comment. There is no uniform way of defining and measuring multimorbidity. Several definitions have been used in literature. Due to self-reported nature of the data, we used 3 as a threshold for multimorbidity to avoid over estimation of the results. References supporting our cut of point have now been added to the revised manuscript.
See page 10 "Similarly, with an a priori assumption that patients on polypharmacy (≥5 different medicines) 34, with multimorbidity (≥3 different medical conditions)35-39 and DBI>0 may have poorer MRB-QoL, we planned to test known group validity of the MRB-QoL if sufficient data were available for these variables."

Comment 7
Results, page 11. In order to fully appreciate the results, it would be interesting if the authors provided more details: 1- Please describe the scale of the questionnaire (results could span from what to what?); 2- Is there a total score, or is the scale used factor by factor? 3- How should clinicians use the scale in clinics? Is there a threshold that should trigger an "alarm" in clinics?

Response
Thank you for this comment. This has now been incorporated in the revised manuscript.
See Page 10 "A conversion formula to transform scores of MRB-QoL scales into a single overall index or total score has been proposed (See supplementary file 2)."
See supplementary file 2 "We proposed the below conversion formula for practitioners and researchers to help them quantify the total burden. Depending on the context and research questions, either selected sub-scale/s or the overall score can be used and computed.

The score ranges from 0 to 100, where, 0 indicates no medication related burden and thus, best possible medication related quality of life. In contrast, 100 indicates the highest level of burden and thus, the worst possible medication related quality of life. However, further evaluation is required in order to determine the cutoff points for MRB-QoL no impact, moderate impact or highest impact on quality of life."

Comment 8
Table 1. Some elements should be included in the Table to ensure it can stand autonomously. The number of individuals should be added in the title. For each variable, please identify that the number reported is a median (as it is stated in the variable age).

Response
The number of individuals has now been added to the title row of Table 1.
See page 11 "Table 1: Characteristics of survey respondents (n=367)."
We reported continuous variables using medians and IQR (e.g. age) whereas categorical variables were reported using frequencies and percentages (e.g. gender, DBI).

Comment 9
Page 15, line 49. "Due to higher levels…" this sentence belongs more in the discussion section than results

Response
Thank you for this comment. This sentence has been deleted from the results section in the revised manuscript

Comment 10
Table 4. Level of statistical significance (alpha value) should be provided with the table. (i.e. A P value <0.05 was considered statistically significant.)

Response
Thank you for the comment. Then P-values have been included in the revised manuscript
See Page 14, Table 4 "**A P Value< 0.001, * A P Value < 0.05"

TYPOGRAPHIC ELEMENTS
Comment 11
Page 4, Strengths and Limitations of this study, line 17: "test-retest" instead of "test-rest"

Response
Thank you for this comment. This has been corrected in the revised manuscript.
See page 4, Strengths and Limitations of this study, line 17 "...MRB-QoL requires further validation such as confirmatory factor analysis, test-retest reliability... "

Comment 12
Page 5, line 34, Unnecessary semicolon after "thus"

Response: Thank you for this comment. The semicolon has been removed in the revised manuscript.
Page 5 "Thus, demonstrating the full picture of the benefit of PC services in improving patients' HRQoL outcomes remains challenging."

Comment 13
On two occasions (lines 10, page 10 and page 15, line 51), "poorer" seems to be misspelled "pooper".

Response: Comment accepted and the word “pooper” has now been replaced with “poorer” in the revised manuscript.
See page 10 “…DBI>0 may have poorer MRB-QoL, we planned to test known group validity…”
See page 15 “… younger patients had higher scores (i.e. poorer quality of life) in all sub-scales than older (>65 years) adults.”

Comment 14
Page 16, Table 5: IQR are reported without decimals except for two results: (<3 conditions and <3 number of medicines); to ensure consistency, we suggest presenting them without decimals.

Response: Comment accepted and these data have now been reported consistently in Table 5 in the revised manuscript.
See page 16, Table 5 “22(14-32)”

Comment 15
Page 21, line 41. However needs a cap H

Response: Comment accepted and correction has now been incorporated in the revised manuscript
See page 21 “However, the Mann-Whitney test is sensitive to detect the differences in distributions between the groups despite the similarity in the median scores”

Comment 16
Page 24, References: Some journal titles are abbreviated and some not.

Response: Comment accepted and inconsistencies in the reference section have now been addressed in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Rhiannon Braund School of Pharmacy, University of Otago, New Zealand
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	As discussed previously this is an important piece of research. The authors have adequately addressed the minor concerns.

REVIEWER	Caroline Sirois Université Laval, Canada I report that one of the authors is a co-investigator on a research grant proposal currently under review for funding.
REVIEW RETURNED	10-Oct-2017

GENERAL COMMENTS	The authors have addressed all issues that were raised. I have no further comments to add.