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

TITLE (PROVISIONAL)	The Work of Being an Adult Patient with Chronic Kidney Disease: A Systematic Review of Qualitative Studies
AUTHORS	Roberti, Javier; Cummings, Amanda; Myall, Michelle; Harvey, Jonathan; Lippiett, Kate; Hunt, Katherine; Cicora, Federico; Alonso, Juan; May, Carl

VERSION 1 – REVIEW

REVIEWER	Valerie Luyckx Institute of Biomedical Ethics and History of Medicine University of Zurich, Switzerland
REVIEW RETURNED	21-Apr-2018

GENERAL COMMENTS	Roberti et al., report their findings of a systematic review of qualitative studies on he “work” of being a patients with chronic kidney disease (CKD). The review has been completed in a systematic manner and an in depth thematic analysis has revealed many issues which as a clinician one knows are relevant and true in many cases. The study is valuable in that it brings together and highlights the challenges faced by CKD patients, which although known my clinicians, are at times overlooked or brushed aside for reasons of time, moral distress on the part of the clinicians or a presumption that these problems are small. The study also has attempted to bring a global perspective to the patient/care giver experience. There are however a few concerns that should be addressed before consideration for publication: 1 The authors claim they have representative data form LMICs, however to may count there are 28 papers from Brazil (with universal health coverage for dialysis), 4 from Mexico, 1 from Nigeria and 1 from India. This can hardly be presumed to reflect experiences of patients in most LMICs. The authors should more clearly state this fact and highlight areas where there is, or is no information from LMIC countries so that gaps in knowledge regarding LMIC are clear. Among the large numbers of papers from Brazil, how many different centres were represented? (and similarly for other countries with many papers), to avoid bias introduced by repeat reporting form the same group of patients on the same topics 2 The authors should be more specific when they are speaking of CKD or dialysis (end-stage kidney disease ESKD) or transplantation. These 3 groups of patients are very different. One gets the impression that in many cases the patient groups are overwhelmingly dialysis patients as their struggles are the toughest. This distinction is important because if this study is to raise

	awareness of patient experiences, it is necessary to understand which challenges are relevant to which groups 3 Relating to points 1 and 2, a summary Table with the main challenges identified would be helpful to orient the reader rapidly, and could include a column for HIC and LMIC with tick marks or +++ signs to illustrate which issues were identified where and potential severity? 4 The title should reflect that this study is limited to adults 5 Line 23 page 3 is incorrect, there are almost 3 million people currently on RRT worldwide. Please update 6 Lines 17-19 on page 10 is grammatically difficult to follow, rewrite 7 Page 11 line 3, what does this statement mean? 8 Page 11 line 8, CKD here clearly is rather ESKD...see comment 2 above. Occurs throughout PRISMA checklist has not page numbers assigned and seems not to contain answers?

REVIEWER	Guillermo Garcia Garcia Nephrology Service, Hospital Civil de Guadalajara FAA University of Guadalajara Health Sciences Center Guadalajara, MEXICO
REVIEW RETURNED	05-May-2018

GENERAL COMMENTS	Thank you for letting me review this intersting and timely paper. I have some comments and questions. It is not clear in the methods how social disadvantaged was defined, especially since 67% of the publications came from high-income countries (HIC),where access to renal replacement therapy (RRT) is universal and only 16% of the publications came from LMIC. Are the publications from HIC limited to disadvantaged populations (ethnicity, immigrants, native, aboriginal populations, etc) in these countries? Additionally, end-of-life decision process and treatment modality selection are practically unknown in the majority of LMIC with resource-constraint access to RRT. Please clearly define in your inclusion criteria if your review was restricted to reports on disadvantaged populations, or avoid using the term "socioeconomic disadvantaged" in the title of the paper. Missing in your review is the paper from Kierans et al (attached) on the challenges faced by uninsured, poor Mexican patients when attempting to access RRT. Using an ethnographic approach, she identified, as you did in your review, structural commonalities among the types of processes found across all cases. Missing in your analysis are the practices of: a) navigating through health and social care structures; b) negotiating treatments and costs; and c) managing formal and informal health information. These practices are commonly found across LMIC and add to the burden of care faced by CKD patients and their families in these countries.

REVIEWER	Hugh Gallagher

	SW Thames Renal Unit St Helier Hospital SM5 1AA, UK
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	This comprehensive, well-structured and very well written systematic review of qualitative studies address the important area of treatment burden in CKD and as such in my opinion represents a significant addition to the existing literature. The methodology described for study selection, data extraction and data analysis appears to be robust. I have just a smaller number of specific comments and suggestions: 1. The majority of the discussion (and all of the illustrative quotations) relate to end-stage renal disease. I note from the Methods and Search Strategy that all stages of CKD were covered within the original searches, but it would be useful to know of the included studies how many were focused on people with (or close to, or unable to access) dialysis and transplantation. 2. Related to this it is likely that the burden of treatment will vary, and progress, across the CKD stages. As the authors recognise CKD is extremely common: for example in the UK around 12-13% of adults have the condition. Most of these people will not develop a progressive decline in their kidney function to a point where renal replacement is required: again in the UK, where the access to RRT is generally recognised to be good, approximately 0.1% are treated with dialysis or transplantation. The burden in the majority with stable kidney disease may be different. Kidney disease commonly co-exists with other conditions such as heart failure and diabetes, and it is possible that there are specific burdens related to multimorbidiity, organisation of care and fragmentation of care. Do the data tell us anything about this? If so this should be discussed fully; if not then I suggest it is made clearer that the focus is on ESRD, particularly in the light of the conclusion that being a person with CKD always implied “high burden, time-consuming, invasive and exhausting tasks”. For a condition where we know a significant proportion are unaware of their diagnosis this cannot be the case. 3. CKD commonly co-exists with depression and I suggest this is also included in the introduction and/or discussion. 4. The fact that in places where there is widespread availability of RRT some people choose not to have RRT (conservative management) might also be mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1.

1. The authors claim they have representative data form LMICs, however to may count there are 28 papers from Brazil (with universal health coverage for dialysis), 4 from Mexico, 1 from Nigeria and 1 from India. This can hardly be presumed to reflect experiences of patients in most LMICs. The authors should more clearly state this fact and highlight areas where there is, or is no information from LMIC countries so that gaps in knowledge regarding LMIC are clear.

Response: We thank the positive comments and suggestions. We have modified the title to reflect the reviewer’s comments about the representation of experiences of patients from LMICs. We have

highlighted that most papers included in the review come from HIC countries and that there are knowledge gaps in LMIC. Knowledge gaps in LMIC are mentioned in the discussion too and supported by the following references:
García-García G, Jha V, World Kidney Day Steering C. Chronic kidney disease in disadvantaged populations. Transplantation 2015
Liyanage, Nimomya, Jha et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet, 2015
Luyckx, Milijeteig, et al Ethical challenges in the provision of dialysis in resource-constrained environments. Sem in Neph 2017
Van Biesen, Vanholder et al. Caring for migrants and refugees with end-stage kidney disease in Europe. AJKD, 2017

2. Among the large numbers of papers from Brazil, how many different centres were represented? (and similarly for other countries with many papers), to avoid bias introduced by repeat reporting form the same group of patients on the same topics.

Response: We have identified the setting reported in each of the included studies and added this information on a new column in the table describing the characteristics of each paper. We have specified number of centres, hospitals and their location. This information can help the reader identify the regions covered in each country represented in this review. In the specific case of Brazil, studies report results from the states of Sao Paulo, Rio de Janeiro, Parana, Santa Catarina, Minas Gerais, Rio Grande do Sul, Paraiba and Bahia.

3. The authors should be more specific when they are speaking of CKD or dialysis (end-stage kidney disease ESKD) or transplantation. These 3 groups of patients are very different. One gets the impression that in many cases the patient groups are overwhelmingly dialysis patients as their struggles are the toughest. This distinction is important because if this study is to raise awareness of patient experiences, it is necessary to understand which challenges are relevant to which groups. Relating to points 1 and 2, a summary Table with the main challenges identified would be helpful to orient the reader rapidly, and could include a column for HIC and LMIC with tick marks or +++ signs to illustrate which issues were identified where and potential severity?

Response: We have made this distinction throughout the text, incorporating ESKD. In the discussion section, we now mention that our results refer mainly to ESKD. In the table with main characteristics of primary studies, we have added a column with "type of patient", with categories "CKD, ESKD, Transplanted". A new table has been added, as suggested by the reviewer with main challenges identified and here we included a column differentiating type of patient (CKD, ESKD, Transplanted), type of country mostly affected (HIC, LMIC), and severity (+, ++, +++). We think that all these additions help the reader to differentiate between CKD and ESKD.

4. The title should reflect that this study is limited to adults
Response: This has been changed as suggested.

5 Line 23 page 3 is incorrect, there are almost 3 million people currently on RRT worldwide. Please update
Response: This has been updated.

6 Lines 17-19 on page 10 is grammatically difficult to follow, rewrite
Response: The sentence has been rewritten for clarity.

7 Page 11 line 3, what does this statement mean?

Response: The sentence has been rewritten for clarity.

8 Page 11 line 8, CKD here clearly is rather ESKD...see comment 2 above. Occurs throughout
Response: This has been corrected in this specific line and, as suggested, corrected throughout the text, with the introduction of ESKD in the first part of the manuscript. Please see point 3 above.

9. PRISMA checklist has not page numbers assigned and seems not to contain answers?
Response: The checklist has been updated again to correct a possible system error.

Reviewer: 2
Reviewer Name: Guillermo Garcia Garcia

1. It is not clear in the methods how social disadvantaged was defined, especially since 67% of the publications came from high-income countries (HIC),where access to renal replacement therapy (RRT) is universal and only 16% of the publications came from LMIC. Are the publications from HIC limited to disadvantaged populations (ethnicity, immigrants, native, aboriginal populations, etc) in these countries? Additionally, end-of-life decision process and treatment modality selection are practically unknown in the majority of LMIC with resource-constraint access to RRT. Please clearly define in your inclusion criteria if your review was restricted to reports on disadvantaged populations, or avoid using the term “socioeconomic disadvantaged” in the title of the paper.

Response: As suggested, we have changed the title of the paper omitting “socioeconomic disadvantaged”. Our review was not restricted to reports on disadvantaged populations but we have identified that BoT of patients with CKD/ESKD was particularly heavy in LMICs, in countries with limited coverage of RRT and in subpopulations in developed countries (such as undocumented migrants in the United States). As you correctly pointed out, most of the research comes from developed countries and this is reflected in the lower percentage of papers from LMICs. We have incorporated a table, as suggested by reviewer 1, describing main challenges and added a column to specify which type of country is mostly affected (high income or LMICs). We have also mentioned this point in the discussion, that our results mainly reflect the experiences of patients in HIC because most of the research included in our review is produced there. Expanding the search strategy to include Spanish and Portuguese languages, we could incorporate primary research published in Latin America (LMICs) that had not been included in previous reviews.

2. Missing in your review is the paper from Kierans et al (attached) on the challenges faced by uninsured, poor Mexican patients when attempting to access RRT. Using an ethnographic approach, she identified, as you did in your review, structural commonalities among the types of processes found across all cases. Missing in your analysis are the practices of: a) navigating through health and social care structures; b) negotiating treatments and costs; and c) managing formal and informal health information. These practices are commonly found across LMIC and add to the burden of care faced by CKD patients and their families in these countries.

Response: We thank the reviewer for signalling this omission. Although Kierans’ most interesting paper had been included in the review, it had not been listed in the table. We have corrected this. Also, using Kierans’ paper as the main reference, we have included, in the results section, a paragraph “navigating through health structures”, which was not a specific category in our results, but as the authors of the ethnographic work pointed out, is an exhausting part of BoT in resource-limited settings. Also, two categories in our results have been expanded to include the analysis of the practices of “negotiating treatments and costs” and “managing information”

Reviewer: 3
Reviewer Name: Hugh Gallagher

This comprehensive, well-structured and very well written systematic review of qualitative studies address the important area of treatment burden in CKD and as such in my opinion represents a significant addition to the existing literature. The methodology described for study selection, data extraction and data analysis appears to be robust. I have just a smaller number of specific comments and suggestions:

Response: We thank the reviewer for his positive feedback on our manuscript.

1. The majority of the discussion (and all of the illustrative quotations) relate to end-stage renal disease. I note from the Methods and Search Strategy that all stages of CKD were covered within the original searches, but it would be useful to know of the included studies how many were focused on people with (or close to, or unable to access) dialysis and transplantation.

Response: As suggested, in the table describing the main characteristics of the included primary studies, we have added a column “type of patient” with the categories “CKD”, “ESKD”, “Transplanted” and their combination, for each paper. In the results section, we have briefly described how many papers covered each of these categories. Throughout the manuscript, we have now differentiated CKD and ESKD as appropriate. Also, as suggested by reviewer 1, we have added a table with main challenges related to burden of treatment with columns describing if each challenged affected patients with CKD, ESKD, or Transplanted, if it mostly affected patients in high-income countries, LMIC or both, and an estimated severity.

2. Related to this it is likely that the burden of treatment will vary, and progress, across the CKD stages. As the authors recognise CKD is extremely common: for example in the UK around 12-13% of adults have the condition. Most of these people will not develop a progressive decline in their kidney function to a point where renal replacement is required: again in the UK, where the access to RRT is generally recognised to be good, approximately 0.1% are treated with dialysis or transplantation. The burden in the majority with stable kidney disease may be different. Kidney disease commonly co-exists with other conditions such as heart failure and diabetes, and it is possible that there are specific burdens related to multimorbidity, organisation of care and fragmentation of care. Do the data tell us anything about this? If so this should be discussed fully; if not then I suggest it is made clearer that the focus is on ESRD, particularly in the light of the conclusion that being a person with CKD always implied “high burden, time-consuming, invasive and exhausting tasks”. For a condition where we know a significant proportion are unaware of their diagnosis this cannot be the case.

Response: We thank the reviewer for this suggestion. Several changes have been made to address this issue: as described in the previous comment, we have differentiated CKD and ESRD in the text to clarify which aspects of treatment burden are specific to being a patient doing dialysis and which relate to being a patient in the early stages of CKD; in the table with characteristics of included papers, we have added a column “type of patient”. Also, we have added a paragraph about the point raised by the reviewer with additional references describing multimorbidity and BoT, and the impact of CKD progression on BoT. Finally, we have specified that our focus was on BoT in patients with ESRD because it is in the end-stage of the disease that BoT is heaviest and, for this reason, most papers report on the experience of patients and their carers in this stage.

3. CKD commonly co-exists with depression and I suggest this is also included in the introduction

and/or discussion.

Response: As suggested, this has been included in the introduction, with additional references.

4. The fact that in places where there is widespread availability of RRT some people choose not to have RRT (conservative management) might also be mentioned.

Response: As recommended, we have mentioned this in the discussion, adding corresponding references.

VERSION 2 – REVIEW

REVIEWER	Valerie Luyckx University of Zurich, Switzerland
REVIEW RETURNED	08-Jul-2018

GENERAL COMMENTS	Now very clear and very insightful paper.

REVIEWER	Guillermo Garcia-Garcia Hospital Civil de Guadalajara Fray Antonio Alcalde, University of Guadalajara Health Sciences Center Guadalajara, Mexico.
REVIEW RETURNED	05-Jul-2018

GENERAL COMMENTS	My comments and suggestions have been properly addressed. Thanks.

REVIEWER	Hugh Gallagher SW Thames Renal Unit
REVIEW RETURNED	05-Jul-2018

GENERAL COMMENTS	Thank you. I am satisfied that this revised version has addressed all areas of concern in my original review.