PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	USE OF THE KIDNEY FAILURE RISK EQUATION TO INFORM CLINICAL CARE OF PATIENTS WITH CHRONIC KIDNEY DISEASE: A MIXED-METHODS SYSTEMATIC REVIEW
AUTHORS	Bhachu, Harjeet; Fenton, Anthony; Cockwell, Paul; Aiyegbusi, Olalekan; Kyte, Derek; Calvert, Melanie

VERSION 1 – REVIEW

REVIEWER	Gunnar Heine Universitatsklinikum des Saarlandes und Medizinische Fakultat der Universitat des Saarlandes, Nephrology and Hypertension
REVIEW RETURNED	07-Sep-2021

GENERAL COMMENTS	Dr Bhachu et al analyze in how far study evidence proves the introduction of the Kidney Failure Risk Equation (KFRE) may change clinical care of CKD patients. They provide a meta-analysis of clinical trials from the last 10 years (e g after KFRE publication) that analyzed clinical implications of KFRE in nephrological daily practice. As a strong proponent of KFRE, I am unhappy to see how few papers have so far tested the clinical implications of KFRE - and I am glad to see that some interventional RCT have been initiated in the meantime. Thus, I am positive that the authors' manuscript will be of interest to clinicians, and merits publication in BMJ open. I have very few requests for changes: > Table 1 is quite difficult to understand for clinicians, and I would propose that the authors briefly characterize each study in the result section as a full text, rather than (or in addition to) the table. Moreover, the table uses terms of biometry that are not really well known among clinicians, so they should double-check their wordings, and some terms need better explanation (eg "mixed-methods"). > I would propose to characterize ongoing RCT in an additional table. > Please consider inviting Dr. Tangri as a Reviewer, if not already done.

REVIEWER	Gregory Hundemer Ottawa Hospital General Campus, Division of Nephrology
REVIEW RETURNED	09-Sep-2021

GENERAL COMMENTS	I would like to thank the editors for allowing me to evaluate the systematic review on the clinical use of the KFRE by Bhachu et al. While the authors were able to identify only a limited numbers of papers that focused on this topic, the paper is nevertheless valuable by combining the results of these prior studies and highlighting the

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	knowledge gaps that still exist on the impact and best use of the KFRE in clinical practice. I do have several comments/questions for the authors to consider: 1. I believe the abstract could be considerably strengthened by adding some of the findings from the systematic reviews from the 5 included studies (even if some are conflicting) particularly in the 3 areas that the authors identified - use of KFRE for a) primary care to specialty care interface, b) general nephrology to multidisciplinary kidney clinic, and c) treatment planning. As written in its present form, not much information can actually be gleaned from the abstract and I think this could be significantly improved. 2. In the Methods section when listing the inclusion criteria, I think more description is required for the 4th criterion "evaluated the actual rather than theoretical impact of utilising the KFRE in clinical practice". This comes across as vague and should be more clearly described. I was left uncertain of what this meant until I read the results section describing which studies were included which then became more clear to me. 3. The authors do a nice job in the discussion outlining the limitations in the existing literature and future studies (several of which are ongoing) that should help further clarify this issue.

REVIEWER	Jia Liang Kwek Singapore General Hospital, Department of Renal Medicine
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	KFRE has been well validated in multiple population The question of clinical utility of risk prediction model is an important one, but current published studies on clinical utility of KFRE are limited. There are diverse interests in the ’clinical utility’ of KFRE and these wide-ranging interests makes performing systemic review on KFRE challenging Even though this manuscript is mainly descriptive/narrative in nature, it is generally well written and follows the PRISMA checklist My 2 questions: (pg 2) Abstract: Rationale and Objective - 'This study aimed to evaluate the evidence base for the utility of KFRE in clinical practice.' Please consider amending it to '...the impact of the utility of KFRE in clinical practice' to more accurately the primary aim in stated in the main text (pg 5 line 54) (pg 31) Flow diagram – reports retrieved: Full test (n=2), conference abstract only (n=3) – please specified which of the 3 articles had only conference abstracts obtained, how that will affect the analyses of these studies, and was there attempt to obtain more information from the authors of these articles?

REVIEWER	Rupert W Major University of Leicester, Health Sciences
REVIEW RETURNED	27-Sep-2021

GENERAL COMMENTS	Thank you for asking me to review this manuscript by Bhachu et al. Overall, it it a concise and clearly written manuscript that investigates an important issue within the CKD disease area. It uses appropriate methods such as pre-registration of protocol, double review of abstracts with arbitration and does not try to

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	inappropriately meta-analyse any of the results. I have the following minor, correctable comments: 1. Please change ESRD to ESKD throughout. 2. Please define "renal replacement therapy" 3. "Data Extraction and Quality Assessment" - please clarify that the "strength and limitations" are those identified by the authors of the identified manuscripts and not your own. 4. Table 2 might benefit from an addition of a column describing the size of the studies (where available) 5. General nephrology to multidisciplinary/advanced kidney care clinic - Line 40 - does it specify the eGFR formula used. 6. Interpretation of the results in the context of other evidence - "Previous studies exploring the potential impact of applying the KFRE at the primary care-specialty care interface suggested it could increase referral number". Not all these studies suggested an increase in referrals and it may be threshold based. Please clarify this. 7. Implication of the results for practice, policy, and future – Can you clarify the fourth of the four trials you identify is the one referred to in “We presented one of the three studies in this systematic review” (ref 32)? 8. Reference 33, please update for published guidelines (published after submission of manuscript). Kind regards, Dr Rupert Major University Hospitals and Leicester and University of Leicester

VERSION 1 – AUTHOR RESPONSE

1. **<u>Response to reviewer 1</u>**

Table 1 is quite difficult to understand for clinicians, and I would propose that the authors briefly characterize each study in the result section as a full text, rather than (or in addition to) the table. Moreover, the table uses terms of biometry that are not really well known among clinicians, so they should double-check their wordings, and some terms need better explanation (eg "mixed-methods").

Response: Many thanks for these comments. Each included study has now been briefly described in the “Results” section in addition to Table 1 which is still present as it does provide some extra detail. The information in Table 1 has been reviewed to ensure clarity of terms and wordings used. The term “mixed-methods” has been explained further in the “Study characteristics” section in “Methods”.

I would propose to characterize ongoing RCT in an additional table.

Response: Additional table added “Table 3” to list the ongoing RCTs.

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2. Response to reviewer 2

1. I believe the abstract could be considerably strengthened by adding some of the findings from the systematic reviews from the 5 included studies (even if some are conflicting) particularly in the 3 areas that the authors identified - use of KFRE for a) primary care to specialty care interface, b) general nephrology to multidisciplinary kidney clinic, and c) treatment planning. As written in its present form, not much information can actually be gleaned from the abstract and I think this could be significantly improved.

Response: Thank you for this comment. Findings from our study have been incorporated into the "Abstract".

2. In the Methods section when listing the inclusion criteria, I think more description is required for the 4th criterion "evaluated the actual rather than theoretical impact of utilising the KFRE in clinical practice". This comes across as vague and should be more clearly described. I was left uncertain of what this meant until I read the results section describing which studies were included which then became more clear to me.

Response: Thank you for this comment. I have changed the word "theoretical" to "potential" which hopefully makes the 4th criterion sound clearer.

3. Response to reviewer 3

(pg 2) Abstract: Rationale and Objective - 'This study aimed to evaluate the evidence base for the utility of KFRE in clinical practice.'

Please consider amending it to '...the impact of the utility of KFRE in clinical practice' to more accurately the primary aim in stated in the main text (pg 5 line 54)

Response: Many thanks for this comment, the sentence in the abstract has now been amended.

(pg 31) Flow diagram – reports retrieved: Full test (n=2), conference abstract only (n=3) – please specified which of the 3 articles had only conference abstracts obtained, how that will

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affect the analyses of these studies, and was there attempt to obtain more information from the authors of these articles?

Response: Thank you for this comment. I have added to Table 1 if studies included were full text or conference abstracts. We have not contacted the authors of the studies and recognise this as a limitation for the analysis with the reduced data and information available to us; this detail has been added to the Discussion, “Limitations of the evidence included in the review and the review process”.

4. Response to reviewer 4

1. Please change ESRD to ESKD throughout.

Response: This has been corrected throughout the manuscript.

2. Please define "renal replacement therapy"

Response: This has now been defined in the study inclusion criteria.

3. "Data Extraction and Quality Assessment" - please clarify that the "strength and limitations" are those identified by the authors of the identified manuscripts and not your own.

Response: Thank you for this comment. I can confirm the “strengths and limitations” as described in the “Data Extraction and Quality Assessment” are regarding the individual identified studies themselves; findings are provided in the Table 2 (Results). Our own study strengths and limitations are given in the Discussion.

4. Table 2 might benefit from an addition of a column describing the size of the studies (where available)

Response: The size of the studies has already been included in Table 1 where data was available.

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5. General nephrology to multidisciplinary/advanced kidney care clinic - Line 40 - does it specify the eGFR formula used.

Response: The studies did not specify which eGFR formula was used; this detail has been added to the manuscript.

6. Interpretation of the results in the context of other evidence - "Previous studies exploring the potential impact of applying the KFRE at the primary care-specialty care interface suggested it could increase referral number". Not all these studies suggested an increase in referrals and it may be threshold based. Please clarify this.

Response: Thank you for this comment. I have clarified this sentence as different risk thresholds will have an affect on the referral numbers, therefore this may not allow for direct comparison between studies.

7. Implication of the results for practice, policy, and future – Can you clarify the fourth of the four trials you identify is the one referred to in "We presented one of the three studies in this systematic review" (ref 32)?

Response: Thank you for this comment. The fourth of the four trials, with details described in the protocol paper by Hemmelgarn et al. (ref 32 in first submitted manuscript), is a multiphase mixed-method study. The findings from Phase 2 of this trial have been published by Smekal et al., which is a study meeting the criteria for inclusion in this systematic review.

8. Reference 33, please update for published guidelines (published after submission of manuscript).

Response: Many thanks, this has now been updated.

VERSION 2 – REVIEW

REVIEWER	Rupert W Major University of Leicester, Health Sciences
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	Thankyou for the updated manuscript. I can confirm that all the issues I raised have been appropriately addressed. Best wishes, Dr Rupert Major, University of Leicester

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