BMJ - Decision on Manuscript ID BMJ.2015.027121

Body: 15-Aug-2015

Dear Dr. Hippisley-Cox,

Manuscript ID BMJ.2015.027121 entitled "Development and validation of risk prediction equations to estimate future risk of blindness and lower limb amputation in patients with diabetes: cohort study."

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=4e939b7795434cc5bee6cf632d1a2b77

Yours sincerely,

Rebecca Burch, MD
Associate Editor, The BMJ
rburch@bmj.com,

Decision: provisional acceptance

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

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If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Wim Weber (Chair), Doug Altman (statistician), Rubin Minhas, Tiago Villanueva, Georg Roeggla, Jose Merino, Rebecca Burch.

Decision: provisional acceptance

Detailed comments from the meeting:
First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

*Editors pointed out that these conditions are not seen very often in the UK anymore, but are much more common in other parts of the world (including the US) and thus this does have wider clinical relevance. (The units for HgA1c are also different in the US, which should be considered in the reporting of these data.) These are also very serious complications and thus are of interest to clinicians.

*Editors wondered about the clinical usefulness of the risk prediction, however, since there's not much that can be done to prevent these complications.

*We would like to see a hyperlink to the risk calculator in the paper itself.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
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Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please

give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
The Authors have developed and externally validated risk prediction equations to quantify the absolute risk for blindness and lower limb amputation in patients with diabetes, at 10 years.
The methodological approach adopted is well designed and applied. Equations, with a double external validation, show robust results. The methods description is clear and easy to follow.
Reasons to conduct the study and provide patients and doctors of a prediction tool are well discussed. Data sources are reliable and currently used in observational studies.
Results are of practical interest for clinicians. The identified predictive tool could be used for better stratifying patients according to their individual risks.

As general comment, I would stress in discussion the problems of generalisability to other countries with different epidemiological patterns.

I have got only minor comments.

Abstract
- Measurement: Mortality is listed beside hospital and GP electronic records as a source to measure incident diagnoses of blindness and amputation. This choice seems weird. How mortality record can contribute in identifying amputations and, specially, blindness? As clearly stated in Methods, ONS provides data on survival, for censoring observation. If ONS is also used for identifying diabetes cases and complications, it should be clearly stated. The role of ONS for identifying the study outcomes, if any, should be clarify. (Same comment for the paragraph 2.2 in Methods).
- Methods (pag. 3): among the listed measures I would substitute sensitivity with accuracy, as we are interested in both sensitivity and specificity.

Introduction
Beside the cited UKPDS model, other models provide estimate of risk of microvascular complications. For example, the CORE Diabetes Model provides simulation of amputation and several models (CORE diabetes model, EAGLE model and Sheffield Diabetes model) provide risk estimates for retinopathy rather then blindness. Such literature should be mentioned as relevant background. Accordingly, in Discussion (4.1 Key findings), the estimated equations cannot be considered the first in predicting blindness and amputation. Such statement should be rephrased to better position the study contribution within the existing evidence. Mostly, to provide a tool to easily calculate the mentioned risks.

Methods
For international readers, the Egton Medical Information System and the Read codes are not straightforward. Please, provide a concise explanation.

The acronym OPCS is not fully explained at its first use.

In the predictor variable identification, is there any cut-off time point for variables based on the latest information recorded in the primary care record before entry to the cohort?

Methods to identify the clinical events used as predictors (atrial fibrillation, congestive cardiac failure,….) have not been clarified. I would not recommend a detailed list of the criteria/codes, but a generic reference to the data sources used and the time frame searched. Number of years since diabetes diagnosis is also a variable of interest and details on the source should be added (see comments on results).

Derivation of the models:
- Typo in 2.4 (second line): "for" is repeated.
- Reasons to carry out 10 imputation should be clarified as for readers, especially clinicians, it is not meaningful. The same for the criteria used for retaining variables (<0.80 and >1.20).
- What is intended with "plausible" in examining interactions?

Results
The high percentage of newly diagnosed patients is not easily justifiable. A comment should be provided. Still, from the table is not clear if there are missing data on this variable.

When listing the amount of missing data for the different variable, cholesterol ratio should be added.

Is there any explained reason for the difference in recording ethnicity and HBA1c among QResearch and CPRD? Provide a comment.

The paragraph 3.3 Primary outcome of amputation and blindness: Description in the text of absolute number of events is not of great interest. I suggest to describe the relative measures and to highlight the relevant differences, where present (e.g lower blindness among men in CPRD versus QResearch) .

3.4.1. Lower limb amputation: The effect of smoking should be described.

3.5.1Validation results for QResearch are not so similar to those of the CPRD cohort, as stated. Even if a formal statistical difference is present only for amputation (ROC statistic both in women and men), all the point estimates of the indicators are lower in QResearch. Authors should comment this result even if it does not change the overall

discussion.

The last paragraph of Methods (beginning of pag.15) should be detach from the previous by adding a specific title (e.g. 3.6 Implementation).

Discussion
Overall, I recommend a more exhaustive reference to the literature in the filed of predicting models. The last sentence of the 4.1 Key findings could be changed into "the fist tool for predicting…".

4.3 Comparisons with the literature, last sentence "However, as previously reported,…" Data seem not to support the statement as smoking was not included in the final models. Rather, it was included in the amputation models. Could it be a typing error?

Figure 4 and 5. Are not easy to understand. Please add the y-axis label.

As the outcomes identification was mainly based on Read codes (used by UK general practice), I am not familiar with them and I was not able to judge the selection provided by the Authors.

Additional Questions:
Please enter your name: Eva Pagano

Job Title: Health economist

Institution: Città della Salute e della Scienza Turin Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
The authors are treading a well-worn path having developed numerous risk scores from the QRESEARCH database. Risk scores for blindness and lower limb amputation have been developed , internally validated and externally validated on very large datasets.

The methodology is strong and the authors adhering to recommended practices in developing and validating risk scores. The authors have also carefeully followed the TRIPOD reporting guidelines for prediction models.

My comments are minor.

Abstract. Make it clear that the patients come from the UK.

Page 9/Page 10: Multiple imputation. Some more information would be useful, whether in the main paper or in supplementary material, that includes what variables were included, any transformations etc.

Page 10. Confirm that the Area Under the Receiver Operating Characteristic Curve has been calculated for survival data (and not for binary outcomes).

Page 10. Why are thresholds of 10% and 20% chosen? Is this for illustrative purposes only? If these are thresholds recommended by the authors then some rationale would be needed. Alternatively, the authors could produce net benefit curves (decision curve analysis, Vickers et al 2006; Med Decis Making) to examine this.

Page 11. Whilst missing data is mentioned for particular variables, how many of the cohort had complete data (or conversely how many had at least 1 missing variable) in the development cohort.

Page 12. Whilst missing data is mentioned for particular variables, how many of the cohort had complete data (or conversely how many had at least 1 missing variable) in the validation cohort.

Page 12. Whilst the authors mention the availability of the risk score at the start of the manuscript. It would also seem a natural place to discuss this in the Results section, preferably with a brief explanation as to why the model is not published in the paper. I know the reasons as to why this is the case, but the average reader won't. The authors are one of the few teams I am aware that actively maintain and update their models on an annual basis, and this should be highlighted as it is a particular strength of these models/group.

Additional Questions:
Please enter your name: Gary Collins

Job Title: Associate Professor

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I led the development of the TRIPOD guidelines for reporting clinical prediction models.