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Dr Jose Merino
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Dear Dr Merino

Manuscript ID BMJ.2018.047010 entitled "Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilisation for respiratory illness in primary care. REDUCE cluster-randomised controlled trial"

Thank you very much for your communication dated 16th November 2018. Thank you also for sending the careful comments of the reviewers and editors on this paper.

We are pleased that you have invited us to resubmit the paper, but we agree that the review comments have raised some important issues. We have now comprehensively revised the paper in order to incorporate the review comments. We provide a point-by-point response on the following pages.

The revised paper now includes an additional Figure (as suggested by the Statistical Reviewer) and an additional Table (as suggested by Reviewer 2). The total word count is now approximately 5,000 words. If required, we will be prepared to edit the paper for length, or to transfer some of this material to the Supplementary data file.

Thank you for considering this revised submission. We hope you agree that these changes have improved the paper.

With best wishes

Yours sincerely

Martin Gulliford

Professor of Public Health

Editorial comments

First, 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.

Thank you, we have now incorporated the suggestions of the reviewers. We now give a point-by-point response below.

*** This is a large, worthy trial. It's not easy to do clinical trials of this size. The paper is quite well written and organized.*

Thank you for this feedback.

*** Our statistician has several queries and his comments are in included below as one of the external reviews.*

Thank you, we now provide a point-by-point response to Prof. Collins' suggestions as outlined below.

*** We wondered about the interpretation, however. The reduction in antibiotic use in intervention practices is modest. Because the effect estimates are very small (and less that what you were originally looking for) and you recruited fewer practices than planned, the conclusions should be more circumspect.*

Thank you for this feedback. However, we suggest that the estimates might not be considered small. The study found an estimated 10-12% relative reduction in antibiotic prescribing for the commonest infections managed in general practice, which are a key element driving antibiotic resistance. This is likely to be important for public health as Reviewer 2 points out. We now comment on the modest nature of the reduction but link this with the potential for public health impact (Abstract): 'Electronically-delivered interventions integrated into practice workflow result in moderate reductions in AB prescribing for RTI in adults, which are likely to be of importance for public health.'

Since this was an open trial, and since we know use of the decision support tool was low, could the demonstrated difference be, at least in part, due to the prescriber knowledge that they were in the intervention group? Please acknowledge this possibility in the discussion.

Thank you, we now comment (page 20): 'It is known that participation in research studies may cause individuals to alter their behaviour.[30] Prescribing feedback delivered to the intervention trial arm might have contributed to heightened awareness of research participation and this might have influenced antibiotic prescribing patterns. It is possible that smaller changes might be observed if prescribing feedback is employed outside of the context of a research study.'

What was the impact of the change in the analysis plan changed during the study because of lower than expected recruitment?

Thank you for this comment. We decided to adopt an individual-level analysis because we recognised the importance of seasonality, while practices participated in the trial for different periods of time. We also considered it important to include individual-level covariates,

including age, gender and comorbidity, especially for analysis of safety outcomes. We now add additional explanation on pages 14-15, where it now reads: ‘For comparison, the unadjusted rate ratio would have been 0.89 (0.68 to 1.16). An analysis of data aggregated to general practice level, gave a mean difference in age-standardised antibiotic prescribing rate of -0.5 (95% confidence interval -8.2 to 7.2) antibiotic prescriptions per 1,000 patient years. These imprecise estimates resulted from wide variations in AB prescribing between general practices; the data appeared to be over-dispersed with several extreme values. Adjusting for covariates reduced the standard error of the coefficient and this was largely accounted for by adjustment for practices’ baseline antibiotic prescribing for RTI. In a sensitivity analysis, an over-dispersed Poisson model gave an adjusted rate ratio of 0.86 (95%CI, 0.75 to 0.97), which confirmed conclusions.’

*** Please include the unadjusted prescribing rate information (the absolute differences found between groups) in the abstract.*

Thank you we now add (Abstract): ‘AB prescribing rate ratios (RR) were: unadjusted, 0.89 (0.86 to 1.16); and adjusted, 0.88 (95% CI, 0.78 to 0.99, P=0.04).’ The absolute measures are also referenced, where it says: ‘AB prescribing rates of 98.7 per 1,000 patient-years for AMS (31,907 AB prescriptions) and 107.6 per 1,000 for usual care (27,923 AB prescriptions).’

*** We don't feel completely reassured about safety when I look at the Forest plot. The point estimates and wide confidence interval for meningitis, empyema, and sepsis worry us. Some of these outcomes are low frequency but have a high impact and we wonder about the ability of a study, even one this large, to provide definitive, reassuring information about safety for individual complications. Please provide more information about the validity of the way in which these outcomes were ascertained. Could serious problems have been missed? What was the time window during which they looked for a subsequent bacterial infection? Some bacterial infections can smolder for a long time before becoming clinically apparent.*

Thank you for these comments. We have now introduced these comments (nearly verbatim, we hope you don’t mind) into the Discussion section of the paper on page 19: ‘This study was considerably larger than most previous studies but was nevertheless not designed to provide conclusive evidence concerning the safety of reducing antibiotic prescribing. Even a much larger study might have limited power to evaluate less frequent safety outcomes or vulnerable sub-groups with precision.[7] The confidence intervals for several individual diagnoses including meningitis, empyema, and sepsis were wide because these outcomes are infrequent but nevertheless may have a high impact on affected individuals. Outcomes were ascertained from Read codes recorded in primary care electronic records. Additional information might have been obtained through linked hospital records (Hospital Episodes Statistics) but these data were not available for all trial practices. Safety outcomes were evaluated during the 12-month intervention period but some safety events might take longer than this to become apparent.’

*** The data sharing statement is not adequate. We require that authors of clinical trials commit to sharing data upon reasonable request.*

Thank you, we now provide a revised data sharing statement that reads (page 23): 'Requests for access to data from the study should be addressed to the corresponding author at martin.gulliford@kcl.ac.uk. The study protocol has been published. All proposals requesting data access will need to specify how it is planned to use the data, and all proposals will need approval of the trial co-investigator team, and CPRD before data release.'

Reviewer: 1

This is a very well-presented manuscript - clearly written, well-informed, appropriately self-critical, and with a thoughtful discussion about the clinical implication of the research findings. The fact that it is transparent in its methodology and results, making it easy for the reader to understand (and the reviewer to point out!) its shortcomings, is a great strength…

Thank you for this feedback.

A common weakness of most cluster randomised trials is the relatively small number of clusters randomised. Eighty is quite a large number in this context but was below the initial target of 120 and only about 25% of the practices approached agreed to participate. The reduction from 120 to 80 practices had only a modest impact in relation to the main outcome (reducing the absolute effect size detectable with 80% power from 15 to 12 prescriptions/1000 patient-years) but I was pleased that in the Discussion section the authors draw attention to the wide confidence intervals around the estimates of harm and mention the implications of the disappointing practice participation rate on generalisability.

Thank you for this feedback.

As the statistical significance of the main outcome is dependent on applying a regression analysis which reduces the standard error, the fact that the authors reported both a sensitivity analysis (an over- dispersed Poisson model) and the main contributory variable to the adjustment (the practice antibiotic prescribing rate) increased my confidence in the result. I also agree with the authors that the observational analysis reported in Table 2 (showing a significant relationship between the antibiotic prescribing rate in intervention practices and the utilisation of the on-line decision support tool) does provide helpful supportive evidence of a causal effect.

Thank you for this feedback.

It will be clear from the above comments that, despite being an old curmudgeon who likes to be critical of the next generation, I like this manuscript very much. However, I think the Abstract should be more circumspect in its statement about safety (An effect estimate of 0.92 with 95% confidence limit of 0.74-1.13 does not justify the bald statement that "Bacterial infections were not increased") and perhaps it would be better if the word "safely" was replaced by "slightly" in the Abstract conclusion.

Thank you, we have modified the wording of the Abstract , so that it now reads: 'There was no evidence that bacterial infections might be increased (RR 0.92, 0.74 to 1.13).'

We also moderated the conclusion (Abstract) as noted above.

Reviewer: 2

This study represents a well-conducted large-scale automated intervention to reduce antibiotic consumption, with a strong and transparently described methodology.

Thank you for this feedback.

Even if the scope of the intervention is limited to respiratory infections, this study can have clear public-health relevance as these indications accounts for an important proportion of inappropriate antibiotic use in primary care. Despite a notably low uptake of the intervention, the results can still be considered promising since a reduction of 12% of antibiotic prescription has been achieved. This study provides some evidence of the possible impact of decision support systems integrated into the practice workflow on improvement of antibiotic use.

Thank you for this feedback.

Nevertheless, some methodological issues need to be explained (14-day time windows) and a broader discussion of some part of the results (impact on specific populations) would be a benefit for the reader.

Strengths of this manuscript include:

- *The design is strong and transparent, and the study is well-conducted*
- *A large population from all over UK is included*
- *The results have clear public health relevance and could also help researchers to design new interventions for antimicrobial stewardship*

Thank you for this feedback. Please see responses below.

Weakness of this manuscript include:

- *Some methodological issues need to be clarified (14-day time window)*
- *Some results need a broader discussion (impact on specific populations, low intake of the electronic tools)*

Thank you, please see response to specific comments shown below.

TITLE: the term "controlled" could be deleted as the term "randomised" already implicates that it is a controlled trial.

Thank you, the word 'controlled' has now been omitted (page 1).

ABSTRACT: Minor comment: It should be mentioned that that automatic monthly feed-back is delivered through a champion.

Thank you, we now add (page 3): ‘Intervention components were delivered electronically, supported by a local practice ‘champion’.’

METHODS:

Major comment: The authors excluded repeat consultations for any RTI during the 14-day time window. Considering that the antibiotic prescriptions included in the primary outcome analysis were those prescribed on the same date of the RTI, it seems that antibiotics prescribed for an RTI after the initial consultation during this 14-day window were not taken into account. As patients may frequently consult a second time for the same symptoms, if they don’t observe any improvement, this time-window could lead to an underestimation of the rate of antibiotics prescribed for RTI. Can the authors explain why they introduced this 14-days window?

Thank you, we now explain (page 10): ‘We determined whether antibiotics were prescribed on the same date as the RTI consultation. In order to focus on prescribing decisions at initial presentations for RTI, repeat consultations for RTI during the same episode were excluded using a 14-day time window.’

We also add: ‘As sensitivity analyses, we evaluated whether estimates differed for a 10-day time window or no time window’. (page 10).

We also now add (pages 14-15): ‘Sensitivity analyses, which compared the base case 14-day time-window for excluding secondary consultations with either a 10-day time-window or no time-window, showed that the effect estimate was not sensitive to whether a time-window was used nor its length (Supplementary Table 1).’

The new Supplementary Table 1 provides results of analyses with either no time window or a 10-day time window. While there are more eligible RTI consultations and AB prescriptions in each trial arm with a shorter time window, the effect estimates are almost unchanged.

The trial analyses have included a 14-day time window, rather than the 10-day time window originally suggested in the protocol. The justification for this is that a 14-day interval will always include four week-end days, while a 10-day interval may variably include either two, three or four week-end days (on which consultations are less likely to occur).

Major comment: The costs of the intervention are not mentioned whereas an economic evaluation was planned in the published protocol (BMJ Open). Has it been performed? If yes, is it planned to provide the results in another publication?

Thank you for this comment. We now provide additional information (page 18): ‘The intervention was delivered at low cost. The budget for the trial was £533,580, which implies that the research and intervention were delivered for less than £1 per patient-year. The marginal cost of extending the intervention to more practices might be lower. Additional analysis found no evidence that overall costs of health care utilisation were different in the intervention and control trial arms.[18]’

Major comment: The presence of the “champion” needs to be clarified. Some additional details on how he/she was recruited, and what exactly his/her role was (re-distributing the e-

mails?) would be good to provide. Can they authors justified why they choose to pass through a champion rather than sending feed-back e-mails directly, since it introduces a supplementary intervention which can be difficult to maintain over time.

Thank you, we now add (page 9): 'General practices were asked to identify a general practitioner as 'champion' for the study, generally the research coordinator at the practice, who ensured that all prescribers were aware of the trial, learned how to use the decision support tools, and received copies of the antibiotic prescribing feedback reports each month.'

Also, can the authors explain why they provided the monthly feed-back at the practice level instead of the prescriber level, since an individual approach may have more impact.

Thank you, we now explain (page 9): 'Data were not analysed at the individual prescriber level because this information is not consistently available within CPRD.'

Major comment: It would be relevant to have more process outcomes, in particular regarding webinar view rate? monthly feed-back: how many GP actually received/opened the monthly feed-back reports? How many GP discussed the monthly feed-back reports during meetings? how many patient information sheets have been printed?

Thank you, we now add (page 17): 'In the intervention period, the number of patient information leaflets printed per practice ranged from zero to 555 with median 54 (interquartile range 7 to 97) leaflets printed per practice.' We also comment (page 21): 'All prescribers also received antibiotic prescribing reports but we were not able to determine whether all prescribers read these each month.'

Minor comment: Mention more clearly the presence of a champion in the description of the feed-back part of the intervention (page 7, line 29)

Thank you. Please see our response shown above. The 'champion' is mentioned in the Abstract and the Print Abstract.

Minor comment: Regarding the collection of safety outcomes, it is mentioned that "linked Hospital Episode statistics data" were not available. What does this mean? Please described it more explicitly since a non-UK audience might not be familiar with these terms.

Thank you for this comment. In order to avoid confusion, this statement has now been deleted. This also avoids duplication, as the point is also made in the Discussion section.

Minor comment: Some examples of what the electronic tools/patient's information sheets looks like provided as supplementary materials would help the reader to have a better idea of the intervention (table and bar-chart in PDF document for monthly feed-back).

Thank you, we have now added four supplementary Figures that provide examples of each component of the intervention. We refer to these in the text on page 9.

RESULTS

Minor comment: Can you provide the number of prescribers per GP practice and the total number of prescribers included in the study?

Thank you, unfortunately it is not possible to resolve prescribing to the individual prescriber level in the present data.

DISCUSSION

Major comment: The difficulty to achieve initial sample size raises some concern about the sustainability of the intervention. Can the authors elaborate on that, since that might threaten the perspectives to implement such intervention at a larger scale?

Thank you, we have now extended our discussion of this point on page 19, where it now reads: 'We also note that only one quarter of eligible general practices agreed to participate in the trial, and if this level of uptake were to be replicated in any future intervention roll-out, then any possible population benefits would be proportionately smaller.[29] The trial continued over 12-months and the trial did not provide evidence concerning any possible longer term outcomes.'

Major comment: The very low intake of the intervention by GP raise concerns about sustainability of the intervention and need a broader discussion. I understand that the patient's leaflet and decision support tools only appeared on the screen if an RTI diagnostic code was entered by the GP. Since the RTI codes might only be entered at the end of the consultation, when the patient already left, did the authors consider displaying the tools when an antibiotic prescription is initiated instead? Or was the process different?

Thank you, we now acknowledge this as a limitation (pages 20-21), where we now say: 'Decision-support tools were necessarily triggered when prescribers entered medical codes into the practice system but some GPs may record data after the end of the consultation, or may rely on free-text entries, reducing the immediacy of this component of the intervention but this post-consultation exposure might contribute to the impact of the intervention over time.'

Minor comment: "Antibiotic prescriptions coded to respiratory indications represented a minority of prescriptions". Please provide the results you are referring to in the results section (which rate of antibiotic prescriptions were coded to respiratory indications and which type of respiratory indications)

Thank you, in order to confirm that this sentence refers to the main results. we modified the wording to read (page 18): 'Antibiotic prescriptions that are clearly associated with a documented RTI represented a substantial proportion of prescriptions, but nevertheless a minority consistent with another recent study,[28] since an appreciable proportion of antibiotic prescriptions are associated with non-specific medical codes or with no code recorded.'

Reference 18 was not accessible on-line

Thank you, reference 18 is 'in press', though we asked the Health Technology Assessment (HTA) Programme to hold back publication pending the outcome of this main paper from the report.

Supplementary table 1: I would put it as a table rather than supplementary material since it describes in detail the intervention.

Thank you for this suggestion, this Table has now been moved to the main text of the paper.

In the content of the antibiotic prescribing report, it is mentioned that results are accompanied by commentary. What kind of commentary is it and by who is it made? Please specify if it is manual or automatized, since a non-automatized process would reduce sustainability.

Thank you, we have now added additional text to Table 1 that explains 'Automated calculation of estimates written into a template using a program written in R.' We also provide an exemplar of the prescribing report in Supplementary Figure 1.

Reviewer: 3 (statistical consultant)

The authors report on a neat and novel design, which was conducted using CPRD contributing general practices. My comments are minor and relate to reporting and clarification.

Thank you for this feedback.

Outcomes: Do we need exact READ codes? Without them, the outcomes are not reproducible.

Thank you, we now provide a code list as supplementary data (uploaded Excel spreadsheet).

Can the authors comment on the lack of factoring in clustering in to the sample size calculation (unless I missed it)? Sample size was changed (at some unspecified point – when?). Initially looking at a 12 (per 1000) reduction requiring 120 practices. Was recalculated now looking for a 15 (per 1000) reduction, requiring 80 practices. Some more hand holding on the sample size calculation would be useful – I can't replicate this, what about cluster size, number of clusters. Some more information on why these new estimates for the new sample size would be useful.

Thank you for this comment. We now explain that the sample size calculation was based on analysis of data aggregated to the cluster (general practice-level), so there was no clustering beyond this. We also clarify (page 11): 'The sample size calculation was based on analysis of outcomes aggregated to cluster-level; it was informed by data from our previous eCRT trial[15] in CPRD. The distribution of general practice-specific AB prescribing rates had a mean 111.9 (SD 39.8) AB prescriptions per 1,000 registered patients, with a correlation coefficient

of 0.82 between AB prescribing in the baseline and intervention periods. We initially aimed to recruit 120 CPRD general practices. Based on analysis of covariance, this would have enabled the study to detect an absolute reduction in antibiotic prescribing for RTI of 12 per 1,000 registered patients. During the recruitment phase of the trial, this target was not achieved because of declining numbers of general practices using 'Vision' software contributing to CPRD. An updated sample size calculation on11th July 2016 found that that a revised total of 80 practices would give 80% power (with alpha 0.05) to detect an absolute reduction in AB prescribing rate of 15 per 1,000 registered patient years.'

Table 1: Some differences in number of patients in each arm, the baseline AB prescribing rate is quite different (lower in the intervention arm)

Thank you, we now provide additional explanation (page 20), where we now say: 'In our previous study, allocation was stratified by practice list size and region[15] but in this trial allocation was stratified by antibiotic prescribing fourth and region. Consequently, there was very good balance between trial arms for baseline antibiotic prescribing for RTI but trial arms were less well balanced with respect to practice list sizes. However, the range of practice list sizes was similar in both trial arms.'

Figure 2 has the primary outcome results (along with various pre-specified subgroups), why not analyse the interaction of treatment with age, but treating age as a continuous variable, and modelled appropriately, possibly using splines. This would be more efficient than arbitrarily categorizing age.

Thank you for this suggestion. We now present a new Figure 4 in which empirical data for antibiotic prescribing is presented by single year of age for each trial arm, with fitted lines plotted using third-degree polynomials. Alongside this, we present estimates from a fully-adjusted model with age-continuous included as a third-degree polynomial, as suggested by the reviewer. These two plots confirm reduced antibiotic prescribing in the intervention trial arm between about the ages of 15 and 85 years. We agree that this method of visualising the data enables more transparent reporting.

We describe the methods for the new plots on page 12: 'Data were visualised by calculating antibiotic prescribing rates for RTI by single year of age and fitting smoothed curves using third-degree polynomials. These empirical data were compared with estimates from a fully-adjusted random effects Poisson model incorporating a third-order polynomial term for age and the interaction with trial arm, with age 15 years was used as reference.'

We also comment in the results section on page 16: 'Figure 4 (left panel) presents empirical data for antibiotic prescribing rates for RTI by single year of age. Fitted polynomial curves suggest that from the late teens to the early eighties antibiotic prescribing for RTI was lower in the intervention trial arm but there was no evidence of reduced antibiotic prescribing in children or very old people. Estimates from the fully-adjusted regression model (Figure 4, right panel) show the same pattern of effect with evidence of reduced AB prescribing in the intervention trial arm from the late teens to early eighties. Data were sparse at very advanced ages with few than 500 patient-years' follow-up at any single year of age over 90 years.'

Table 2: 'Quartile' – should be 'fourth'. Quartiles are cutpoints to create 4 equal sized groups.

Thank you, 'quartile' has been changed to 'fourth' throughout.

Flow diagram could be improved (following the CONSORT cluster flow diagram), including reporting how many were analysed etc.

Thank you, we have now updated the flowchart to show the numbers of general practices, and numbers of registered patients included at each stage of the study as required by the CONSORT extension for cluster randomised trials. The CPRD population is dynamic, with patients moving in and out of practice registration, but patient populations were counted during the baseline period.

Editorial requirements

1. What this paper adds/what is already known box.

Please see page 5.

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part.

Please see page 8, first paragraph: 'The protocol was approved by the NHS London-Dulwich research ethics committee and by the CPRD Independent Scientific Advisory Committee (ISAC 14_130).'

3. Patient confidentiality forms when appropriate

Not applicable.

4. Competing interests statement

Please see page 23.

5. Contributorship statement+ guarantor

Please see page 23.

6. Transparency statement

Please see page 24.

7. Copyright statement/licence for publication

Please see page 24.

8. Data sharing statement

Please see page 23.

9. Funding statement and statement of the independence of researchers from funders

Please see page 23.

10. Patient involvement statement

Please see page 13.

11. Please ensure the paper complies with The BMJ's style, as detailed below:

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

Included page 1.

b. Abstract: Please include a structured abstract with key summary statistics, as explained below

Included page 2.

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

Please see pages 6-7.

d. 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.

Please see Page 9, Table 1 and Supplementary Figures 1 to 4.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines

We believe that these requirements have been met.

i. 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.)

Please see Abstract: 'AB prescribing was reduced in adults aged 15-84 years (RR 0.84, 95%CI 0.75 to 0.95), with one antibiotic prescription per year avoided for every 62 (40 to 200) patients.'

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

Please see Figure 3 for absolute event rates,

Please report all outcomes that were listed in the trial registry, or explain that you will publish them elsewhere. Please clearly identify each outcome as primary, secondary, or post-hoc in

the text, abstract, and any tables or figures. We expect authors to report prespecified outcomes. If outcomes in the trial registry have later been changed, please explain the reasons for the change and the dates of the change in the paper. You may report the changed outcomes, but we will expect you to also report on the originally specified outcomes unless otherwise agreed with the handling editor for your paper.

Occasionally the outcomes that are prespecified in a trial registry do not match up with those included in the trial protocol. When there are discrepancies between protocol and registry specified outcomes, we expect the paper to report and interpret the registry specified outcomes. You may also report any protocol specified outcomes, but if you do please be sure to include the date of the protocol and the point at which each outcome was added to the protocol, and explain why the registry entry differed from the protocol and why the registry was not updated to reflect any protocol changes.

All outcomes that were specified have been presented either in the main text or in the supplementary materials.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

Thank you, the Discussion section has been revised and sub-headings incorporated.

g. Footnotes and statements

The research is funded by the NIHR and a CC-BY licence is required please.