Subject: BMJ - Decision on Manuscript ID BMJ.2018.047010

Body: 16-Nov-2018

Dear Prof. GULLIFORD

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 for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Jose Merino
jmerino@bmj.com

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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: Elizabeth Loder (chair), Gary Collins (statistician), Daoxin Yin, José Merino

Decision: Put points

Detailed comments from the meeting:

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.

Please also respond to these additional comments by the committee:

** 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.

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

** We wondered about the interpretation, however. The reduction in antibiotic use in intervention practices is modest. 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. 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. What was the impact of the change in the analysis plan changed during the study because of lower than expected recruitment?

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

** 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.

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

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

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.

As the main author suggests in his letter, the BMJ might wish to consider publication not just on the basis of the clinical importance of the research findings but on the innovative methodology. There is considerable interest in how the strengths of the clinical trial method can be aligned to the “big data” recoverable from electronic records. The manuscript describes a creditable attempt to achieve this – cluster randomising 80 UK general practices from across the UK to receive the intervention, collecting patient-based outcome data from electronic patient records, and using Poisson regression to adjust for pre-specified baseline differences between the randomisation arms (to reduce the variability around the effect estimate introduced by the methodological weakness of cluster randomisation) while still applying an ITT analysis.

The intervention assessed was appropriately theory-based but simple – identification of a GP from each practice to support the intervention, electronic prescribing guidance for GPs,

monthly feedback on practice prescribing rates, and information for GPs to distribute to individual patients (presumably to explain the reason for non-prescribing).

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.

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.

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.

David Mant

Additional Questions:
Please enter your name: David Mant

Job Title: Emeritus Professor of General Practice

Institution: Oxford University

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

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laration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I have worked in the past, and published, with four of the authors of this paper (but not the main author)

Reviewer: 2

GENERAL COMMENT

This cluster-randomised trial aims to assess the effectiveness and safety of a multicomponent decision support tool that is electronically delivered to general practice. The support system aims to avoid unnecessary antibiotic prescriptions for self-limited respiratory infections in a population of patients consulting GPs from all over UK.
This study represents a well-conducted large-scale automated intervention to reduce antibiotic consumption, with a strong and transparently described methodology.
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.
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

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)

Given these limitations I would recommend a major revision.

Specific comments by section

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

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

INTRODUCTION:
No comment

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?
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?
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. 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.
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?
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)
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.
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).

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

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?
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?
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)

REFERENCES:
Reference 18 was not accessible on-line

TABLES AND FIGURE

Figure 1: no comment
Table 1: no comment
Supplementary table 1: I would put it as a table rather than supplementary material since it describes in detail the intervention. 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.

Gaud Catho AND Benedikt Huttner

Additional Questions:
Please enter your name: Gaud Catho

Job Title: MD

Institution: Geneva University Hospitals

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

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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.

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

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. Can

the authors comment on the lack of factoring in clustering in to the sample size calculation (unless I missed it)?

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

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.

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

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

Additional Questions:
Please enter your name: Gary Collins

Job Title: Professor of Medical Statistics

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

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