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)	An Economic Analysis of Oral Dexamethasone for Symptom Relief of Sore Throat: The UK TOAST Study
AUTHORS	Burns, Richeal; Wolstenholme, Jane; Jawad, Sena; Williams, Nicola; Thompson, Matthew; Perera, Rafael; Hay, Alastair; Heneghan, Carl; Little, Paul; Moore, Michael; Hayward, Gail

VERSION 1 – REVIEW

REVIEWER	Walter Lehmacher Institute of Medical Statistics, Informatics and Epidemiology University of Cologne Germany
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	Table 3 indicates that in the Dexa group less costs for antibiotics are payed. Beyond the costs, is there a medical advantage in the sense that a reduction of antibiotics is possible. Some words to this problem would be interesting.

REVIEWER	Peter Wilson University College London Hospitals, UK
REVIEW RETURNED	19-Oct-2017

GENERAL COMMENTS	This is a good quality study from an experienced primary care research group. The paper is based on an economic analysis of a double-blind study but it was unclear if there are other publications associated with the study. In the abstract line 18 I would suggest not saying the impact was negative if not statistically negative. The more important outcome is the finding of benefits associated with delayed prescription. The latter is currently advocated as a means of reducing antibiotic use. In the introduction, there is no mention of direct antigen testing for Streptococcus group A as a means of reducing unnecessary antibiotic use. What is the effect of the use of steroid on carriage of Streptococcus group A afterwards? Effects on antimicrobial resistance are more likely to be seen if amoxicillin use is reduced rather than penicillin. In the methods line 22 details of the adverse event should be provided as it was sufficient to alter the protocol. As completion of the diaries was a problem, the efforts made to ensure patients complied should be described.

	P8 Although published costs are used for drug costs, locally negotiated prices usually apply although it is mentioned there was no discounting. The economic analysis otherwise seems to be robust. The main benefit was associated with delayed prescription rather than dexamethasone. Nevertheless, the cost effects were modest and variable. The reasons for the benefit should be more closely examined in the discussion – were the increased health service uses due to persistent symptoms, proven Group A streptococcal infection or spread to household contacts? The 60% compliance with diary completion was low and the risk of bias must be high. Was there any collateral information available on those not completing the diary to suggest they differed? In Table 4 the scenarios should be more clearly explained.

VERSION 1 – AUTHOR RESPONSE

Manuscript ID bmjopen-2017-019184 entitled "An Economic Analysis of Oral Dexamethasone for Symptom Relief of Sore Throat: The UK TOAST Study" which you submitted to BMJ Open, has been reviewed. The comments of the reviewers are included at the bottom of this letter.

- Response to reviewers' comments:

Editorial Requests
A1.
Please add headings to the various sections included at the end of the paper on pages 17-18 (competing interests, data sharing statement etc.).
Response: We thank the editor for highlighting this and have updated as requested.

A2.
Please add an ethics statement to the methods section of the manuscript.
Response: The following was added to the methods section:
The research protocol was approved by the National Research Ethics Committee South Central (12/SC/0684).

Reviewer 1
B1.
Table 3 indicates that in the Dexa group less costs for antibiotics are payed. Beyond the costs, is there a medical advantage in the sense that a reduction of antibiotics is possible. Some words to this problem would be interesting.
Response: We thank the reviewer for the comment and agree that the economic and societal benefits of reducing antibiotic exposure and therefore resistance are critically important; however they are also very challenging to estimate and there is little literature to support this approach within cost effectiveness analysis. Furthermore the absolute reduction in antibiotic use was small in this trial, and the trial was not powered on this outcome measure. We have now mentioned this issue in the discussion as follows:

Although only a slight reduction in antibiotic usage was observed in the intervention arm relative to the placebo i.e. 3% less reported use for the delayed prescription sub-group, we feel the range of budgetary, clinical and environmental benefits of reducing antibiotic usage need to be explored further given the evidence highlighted in this study.

Reviewer 2

C1. This is a good quality study from an experienced primary care research group. The paper is based on an economic analysis of a double-blind study but it was unclear if there are other publications associated with the study. In the abstract line 18 I would suggest not saying the impact was negative if not statistically negative. The more important outcome is the finding of benefits associated with delayed prescription. The latter is currently advocated as a means of reducing antibiotic use.

Response: We thank the reviewer for their remarks. We have referenced the main trial paper, which is currently the only other publication associated with the study, in the introduction. We have now clarified in the introduction the findings of the clinical paper. We have also adjusted the abstract as suggested.

In the abstract (line 17) we removed 'negative but' so the line now reads: "…the impact of the intervention was negative but not statistically significant:…"

In the Introduction section, we have added in a sentence on the trial findings which have been published as follows:
The findings of the trial highlighted no clinical impact of a single dose of oral dexamethasone compared with placebo for resolution of symptoms at 24 hours; however, at 48 hours there was a significant improvement for patients receiving the intervention.

C2. In the introduction, there is no mention of direct antigen testing for Streptococcus group A as a means of reducing unnecessary antibiotic use. What is the effect of the use of steroid on carriage of Streptococcus group A afterwards?

Response: This is an interesting question. However, Strep A testing is not standard care in UK general practice and as it was not directly relevant to the trial question it was not performed in this trial either before or after the intervention.

C3. Effects on antimicrobial resistance are more likely to be seen if amoxicillin use is reduced rather than penicillin.

Response: This was a trial of an alternative to antibiotics in sore throat, for which Phenoxymethylpenicillin and macrolides are standard antibiotic therapy. Therefore amoxicillin use is beyond the scope of this study, Penicillin is by no means a harmless antibiotic despite lack of evidence of resistance in group A streptococcus, Exposure impacts on resistance in other potential pathogens, such as pneumococci and disrupts the host microbiome.

C4. In the methods line 22 details of the adverse event should be provided as it was sufficient to alter the protocol.

Response: We thank the reviewer for highlighting the lack of clarity in the methods section. We have added further detail regarding this adverse event in the footnote referring to it, and added a general note regarding the nature of the SAEs included in the study as follows:
SAEs included in the analysis were those classified as such by the trial protocol; and detailed in the main trial paper.

C5. As completion of the diaries was a problem, the efforts made to ensure patients complied should be described.

Response: Following initial poor diary return rates, a protocol amendment was approved to offer participants a thank you shopping voucher for diary completion. This has now been mentioned in the text. This is summarised in the limitations as follows:
The initial response rate was much lower and a protocol amendment which allowed the use of incentives for patients who returned diaries was introduced.

C6. P8 Although published costs are used for drug costs, locally negotiated prices usually apply although it is mentioned there was no discounting. The economic analysis otherwise seems to be robust.

Response: We thank the reviewer for this observation and realise that the published costs may not represent the costs paid to the NHS due to price negotiations by individual care providers. However, it would be difficult to incorporate the variation in negotiation power across care providers. By using published costs, we are following best practice; furthermore, we feel negotiating power would only effect the cost burden overall and not the incremental differences across trial arms.

C7. The main benefit was associated with delayed prescription rather than dexamethasone. Nevertheless, the cost effects were modest and variable. The reasons for the benefit should be more closely examined in the discussion – were the increased health service uses due to persistent symptoms, proven Group A streptococcal infection or spread to household contacts?

Response: We thank the reviewer for highlighting this issue. Health service use was recorded for the participant and not for their household contacts and as such we do not have details on household contagion and whether or not that was a contributory factor to variation in resource use. Strep A testing is not routinely performed in UK primary care settings and so we do not have evidence to suggest if this was a factor in return visits over the follow-up period. Furthermore, the sub-group analysis that highlighted cost differences should be interpreted with caution given the trial was not powered for sub-group analysis or resource use and the completion rates of 60% would be considered low to average.

We have added in a further sentence to guide readers to interpret the cost differences with caution as follows:
Caution is needed in interpreting this variation as the trial was not powered for sub-group analysis of resource use and response rates were low.

C8. The 60% compliance with diary completion was low and the risk of bias must be high. Was there any collateral information available on those not completing the diary to suggest they differed?

Response: We agree with the reviewer here and unfortunately low response rates with patient self-complete diaries are a recurrent issue in clinical trials. In order to apply appropriate multiple imputation (MI) methods, the missing data had to be examined in detail and the missingness categorised in order to employ the corresponding method of MI. The data was considered missing at random and when the missingness was examined in regression analysis, age was the only contributory factor. In order to attempt to mitigate the impact of the bias a range of potential confounding characteristics were included in the imputation model. This is highlighted in the supplementary files. Apart from the attributes collected in the baseline survey, we do not have any further data on those patients who did not complete the diaries unless they experienced adverse events and returned to the GP within the 28 days of follow-up.

We had added in a further phrase in the limitations section where the multiple imputation techniques are discussed as follows:

…and therefore some bias may remain in terms of the resource use and outcomes reported versus those that were not.

C9. In Table 4 the scenarios should be more clearly explained.

Response: We thank the reviewer for highlighting this issue. A full table explaining scenarios undertaken is included in the supplementary file. I have added a footnote to Table 4 to highlight this to the reader.

VERSION 2 – REVIEW

REVIEWER	Peter Wilson University College London Hospitals UK
REVIEW RETURNED	14-Feb-2018

GENERAL COMMENTS	Thank you for dealing with the comments

Correction: *Economic analysis of oral dexamethasone for symptom relief of sore throat: the UK TOAST study*

Burns RM, Wolstenholme J, Jawad S, *et al*. Economic analysis of oral dexamethasone for symptom relief of sore throat: the UK TOAST study. *BMJ Open* 2018;8:e019184. doi: 10.1136/bmjopen-2017-019184.

This article was previously published with an error.

The statement below should be added in the 'Acknowledgments' section.

This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care.

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