PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Xylitol for the prevention of acute otitis media episodes in children aged 2-4 years: Protocol for a pragmatic randomized controlled trial
AUTHORS	Persaud, Nav; Laupacis, Andreas; Azarpazhooh, Amir; Birken, Catherine; Hoch, Jeffrey; Isaranuwatchai, Wanrudee; Maguire, Jonathan; Mamdani, Muhammad; Thorpe, Kevin; Allen, Christopher; Mason, Dalah; Kowal, Christine; Bazeghi, Farnaz; Parkin, Patricia; TARGet Kids!, Collaboration

VERSION 1 – REVIEW

REVIEWER	Tal Marom, MD Department of Otolaryngology-Head and Neck Surgery, Assuta Ashdod University Hospital, Ben Gurion University Faculty of Health Sciences, 77476 Ashdod, Israel
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	Well written, well designed. Good luck!

REVIEWER	Hasantha Gunasekera University of Sydney, The Children's Hospital at Westmead Clinical School
REVIEW RETURNED	25-Dec-2017

GENERAL COMMENTS	BMJopen-2017-020941 Protocol Review This is a pragmatic blinded two-armed superiority placebo RCT of xylitol vs. placebo sorbitol for 6m duration for the prevention of AOM in 2-4 year old children. The study question is important and the methods are reasonable but I have some comments and suggestions to improve the clarity (see below). Suggestions: 1. Pg13 Line 38: Please explain “we will treat the data as censored” 2. There will be misclassification of AOM, but, with randomisation, it is reasonable to assume the misclassification will be equally distributed in both arms. However, if there is substantial false positive diagnoses of AOM (due to red TMs without effusions being called AOM), the effect of xylitol in preventing AOM would likely be underestimated if it works to prevent AOM or would not reach significance rather than an error in finding a benefit where there is none. 3. SPIRIT Section 5c: What is the involvement of the manufacturer in the concept, design, implementation, data collection and analysis and permission to publish? I don't think it is reasonable to state “N/A” given the potential benefit to the manufacturer if this trial shows a clear benefit of xylitol.

	4. Sensitivity analysis of <36m vs. >36m is a good idea, but also should analyse for number of previous AOM (perhaps xylitol better at reducing episodes in recurrent AOM vs. infrequent AOM?). 5. Insertion of Its prior to enrolment is an exclusion criteria but what if children have surgery while in the trial? Depending on how frequent ENT surgery is in your setting, this might be a worthwhile secondary outcome given the longer than usual follow-up period in this trial. 6. Your data extraction sheet has "(2) Does a chart entry within 48 hours record physical examination findings of the tympanic membrane? [Yes or No]" which is slightly different to the protocol where you state the TM must have signs of AOM (e.g., erythema). The data extraction sheet just asks for a record of the examination, not the actual findings being consistent with AOM. Please ensure actual findings are included and list all the "eligible" findings. I would argue that erythema is a very bad diagnostic criterion as it is so subjective, whereas bulging would be highly suggestive of AOM, redness would not. 7. In relation to the Spiro reference, it showed that adding tympanometry didn't change paediatricians diagnosis of AOM, that is not the same as saying that tympanometry isn't a more accurate way to confirm effusions, including AOM. Indeed, Spiro suggests up to a 40% reduction in AOM diagnoses with the use of tympanometry. I understand your question relates to physician diagnosed AOM, including inaccurate diagnoses, but I think clarification of this issue is important as tympanometry (and/or pneumatic otoscopy) is the current recommendation in many international guidelines, including AAP and the Australian guidelines and lack of tympanometry in your diagnosis definition is a limitation.

REVIEWER	Norhayati Mohd Noor Medical Lecturer, Universiti Sains Malaysia, Malaysia
REVIEW RETURNED	07-Jan-2018

GENERAL COMMENTS	1) Please elaborate on how the participation consent and assent will be taken. 2) There are few very old references #14, #16, #23, #45, #46, #63 Reference #16 on healthcare cost (1976) is far too old. Please replace these articles. 3) Are there any other possible limitations with regards to data collection besides inability of the parents to distinguish AOM from other URTI? 4) Azarpazhooh Amir is the contact person for a Cochrane systematic review "Xylitol for preventing acute otitis media in children up to 12 years of age". Well, this study is also important to provide possible new findings with regards to xylitol in AOM, URTI and dental caries and may add up to the findings of the related systematic reviews.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Tal Marom, MD

Institution and Country: Department of Otolaryngology-Head and Neck Surgery, Assuta Ashdod University Hospital, Ben Gurion University Faculty of Health Sciences, 77476 Ashdod, Israel

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Well written, well designed. Good luck!

***AUTHOR RESPONSE: Thank you for the comment.

Reviewer: 2
Reviewer Name: Hasantha Gunasekera

Institution and Country: University of Sydney, The Children's Hospital at Westmead Clinical School

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
BMJopen-2017-020941 Protocol Review

This is a pragmatic blinded two-armed superiority placebo RCT of xylitol vs. placebo sorbitol for 6m duration for the prevention of AOM in 2-4 year old children. The study question is important and the methods are reasonable but I have some comments and suggestions to improve the clarity (see below).

Suggestions:
1. Pg13 Line 38: Please explain “we will treat the data as censored”

***AUTHOR RESPONSE: We have changed this to missing.

2. There will be misclassification of AOM, but, with randomisation, it is reasonable to assume the misclassification will be equally distributed in both arms. However, if there is substantial false positive diagnoses of AOM (due to red TMs without effusions being called AOM), the effect of xylitol in preventing AOM would likely be underestimated if it works to prevent AOM or would not reach significance rather than an error in finding a benefit where there is none.

***AUTHOR RESPONSE: We have added a discussion of this limitation on page 7.

3. SPIRIT Section 5c: What is the involvement of the manufacturer in the concept, design, implementation, data collection and analysis and permission to publish? I don't think it is reasonable to state “N/A” given the potential benefit to the manufacturer if this trial shows a clear benefit of xylitol.

***AUTHOR RESPONSE: We have updated the manuscript’s funding section: “There was no role of the manufacturer in the concept, design, implementation, data collection and analysis and permission to publish. The products were purchased from the manufacturer using public research funding.”

4. Sensitivity analysis of <36m vs. >36m is a good idea, but also should analyse for number of previous AOM (perhaps xylitol better at reducing episodes in recurrent AOM vs. infrequent AOM?).

***AUTHOR RESPONSE: Unfortunately we will not have information about prior AOM episodes.

5. Insertion of Its prior to enrolment is an exclusion criteria but what if children have surgery while in the trial? Depending on how frequent ENT surgery is in your setting, this might be a worthwhile secondary outcome given the longer than usual follow-up period in this trial.

***AUTHOR RESPONSE: We do not expect a large number of children to have surgery during the study. We will employ an intention to treat analysis. If there happen to be large number of children who undergo surgery, we can perform such an analysis.

6. Your data extraction sheet has “(2) Does a chart entry within 48 hours record physical examination findings of the tympanic membrane? [Yes or No]” which is slightly different to the protocol where you state the TM must have signs of AOM (e.g., erythema). The data extraction sheet just asks for a record of the examination, not the actual findings being consistent with AOM. Please ensure actual findings are included and list all the “eligible” findings. I would argue that erythema is a very bad diagnostic criterion as it is so subjective, whereas bulging would be highly suggestive of AOM, redness would not.

***AUTHOR RESPONSE: Yes the findings must be consistent with AOM. We are using a validated instrument for assessing AOM. The trial manual explains that physical examination findings include both erythema and bulging.

7. In relation to the Spiro reference, it showed that adding tympanometry didn't change paediatricians diagnosis of AOM, that is not the same as saying that tympanometry isn't a more accurate way to confirm effusions, including AOM. Indeed, Spiro suggests up to a 40% reduction in AOM diagnoses with the use of tympanometry. I understand your question relates to physician diagnosed AOM, including inaccurate diagnoses, but I think clarification of this issue is important as tympanometry (and/or pneumatic otoscopy) is the current recommendation in many international guidelines, including AAP and the Australian guidelines and lack of tympanometry in your diagnosis definition is a limitation.

***AUTHOR RESPONSE: We have adjusted the discussion of the Spiro study in the text to indicate that this is a limitation. The other practical reasons for not using tympanometry stand.

Reviewer: 3
Reviewer Name: Norhayati Mohd Noor

Institution and Country: Medical Lecturer, Universiti Sains Malaysia, Malaysia

Please state any competing interests or state ‘None declared’:None declared

Please leave your comments for the authors below
1) Please elaborate on how the participation consent and assent will be taken.

***AUTHOR RESPONSE: Thank you for your comment. We have added this information to the Methods and Analysis section of the manuscript.

2) There are few very old references #14, #16, #23, #45, #46, #63
Reference #16 on healthcare cost (1976) is far too old.
Please replace these articles.

***AUTHOR RESPONSE:
#14, #23 and #46 have been removed and replaced.

#16 has been removed and replaced, and we have added an additional reference, #64.
#45 we have added an additional reference, #65.
#63 has been removed and replaced with #32 and #35.

3) Are there any other possible limitations with regards to data collection besides inability of the parents to distinguish AOM from other URTI?

***AUTHOR RESPONSE: We have added a limitation related to the physician diagnosis.

4) Azarpazhooh Amir is the contact person for a Cochrane systematic review “Xylitol for preventing acute otitis media in children up to 12 years of age”. Well, this study is also important to provide possible new findings with regards to xylitol in AOM, URTI and dental caries and may add up to the findings of the related systematic reviews.

***AUTHOR RESPONSE: We agree that this trial may well provide important information about the secondary outcome of dental caries.

VERSION 2 – REVIEW

REVIEWER	Hasantha Gunasekera The University of Sydney, Australia
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	Thank you, the authors have addressed the comments and suggestions and I would recommend publication. I wish the authors the best of luck with this work!

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2
Reviewer Name: Hasantha Gunasekera

Institution and Country: The University of Sydney, Australia

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you, the authors have addressed the comments and suggestions and I would recommend publication. I wish the authors the best of luck with this work!

***AUTHOR RESPONSE: We appreciate your comments and suggestions, and thank you for your wishes.