

To the Editor-in-Chief of *World Journal of Gastroenterology*

Athens, 8th February 2019

Sir,

We thank you and the reviewers for giving us the opportunity to revise our invited manuscript in the “Meta-analysis” column of your prestigious journal (Manuscript Nr.: 45414, Invitation: UEGW 2018) entitled “Effect of Endocuff use on colonoscopy outcomes: a systematic review and meta-analysis”.

Our manuscript has neither been published nor has been submitted elsewhere for evaluation and all authors have no conflict of interest to declare. All authors have substantially contributed to conception and design, acquisition of data, drafting and final approval of the submitted manuscript version. Please find below a step-to-step response to reviewers’ comments. In the revised manuscript each amendment corresponding to reviewers’ comments is highlighted yellow to facilitate the review process. We hope that the revised manuscript meets your requirements for publication.

Sincerely,

Ioannis S. Papanikolaou, MD, PhD

Associate Professor of Gastroenterology

Reviewer No: 02549032

Reviewer's comment: This is a potentially interesting meta-analysis on the role of the Endocuff for adenoma detection rate. Finally, 9 studies included for analyses. The authors concluded << Effect of Endocuff use on colonoscopy outcomes: a systematic review and meta-analysis >>. However, some major issues are very important:

1. Although the authors stated that their meta-analysis is more accurate than the 3 other recent meta-analyses with the same issue, the conclusion is the same. Actually another meta-analysis with the same articles is too much for this issue. It would be advisable to wait for more information and data from multiple worldwide centers. I can't really understand what was the substantial need of this meta-analysis and what more does the present meta-analysis add to the existing literature?

Authors' response: We would like to thank the reviewer for the valuable contribution. We acknowledge his criticism in the second paragraph of the Discussion section of the amended manuscript, where we extensively describe the differences between our study and existing meta-analyses on this matter. In detail, our study is the only one taking advantage of all currently available published data (with the adjunction of many secondary endpoints) including exclusively all fully published RCTs. Previous meta-analyses included studies of retrospective design (Chin et al 4/9 retrospective studies), analyzed multiple add-on devices including EAC (Facciorusso et al) or finally included data available only in abstract

form [Faccioruusso et al (4/9 abstracts) and Williet et al (5/12 abstracts)]. While we acknowledge colleagues' important contribution in the effort to answer the question regarding efficacy of EAC on colonoscopy outcomes, we believe that our study's strict methodology and inclusion criteria allow us to provide with optimal, safe and generalizable results, tackling any limitation of previous works.

2. One of the major conclusions was negative: <<In terms of AADR and MAC, no difference was detected between EAC and CC>>. So it would be advisable to focus also to this main result in the conclusion of the abstract in order this meta-analysis to be clinically useful in terms of accuracy and objectivity.

Authors' response: We thank the reviewer for the valuable comment. Accepting the criticism, we amended the abstract of our manuscript as proposed (*page 4, Abstract, Conclusion*).

3. We congratulate the authors to discuss about cost-effectiveness although this was not the aim of this meta-analysis. To our knowledge there are no studies on cost-effectiveness in relation to Endocuff use.

Authors' response: We thank the reviewer for the polite comment.

4. Despite the positive conclusions of the present study, Endocuff is not widespread accepted. Did the authors find any possible explanations?

Authors' response: We acknowledge the reviewer's comment. Our study did not aim to elucidate device's market penetration and to the best of our knowledge no

study addressing this matter exists, yet. Additional financial burden and local availability could be reasonable factors answering reviewer's skepticism, but no specific explanations were identified in the studies including in our meta-analysis.

5. We noticed that the majority of references regarding use of endocuff are from the same authors of the present study. 7,8,9,30. Obviously the authors begin with a positive attitude towards the use of endocuff. In order to persuade the international community of the usefulness of this device more data from different centers worldwide are necessary and advisable. Did the authors have any conflict of interest or financial interest?

Authors' response: We would like to thank the reviewer for giving us the opportunity to clarify this matter. Aim of the current study was to evaluate the potential impact of Endocuff use on colonoscopy outcomes through a systematic review and meta-analysis. The latter was performed based on a strict predefined protocol – registered in the PROSPERO database and freely available – and by following established guidelines. Similarly, the results of the study are presented objectively beyond any potential attitude towards the device or previous publications. Moreover, we would like to underline that our group's RCT study (*Triantafyllou K, Polymeros D, Apostolopoulos P, et al. Endocuff-assisted colonoscopy is associated with a lower adenoma miss rate: a multicenter randomized tandem study. Endoscopy 2017; 49(11): 1051-1060; reference 30 in the original submission*) on Endocuff was not included in this meta-analysis as it did not fulfil the prespecified in the PROSPERO registered protocol inclusion criteria (tandem design study). It is used only in the Discussion section as it is the sole tandem RCT on Endocuff in

terms of adenoma miss rate; another important colonoscopy quality indicator. Moreover, reference 8 of the original submission (**Gkolfakis P**, Tziatzios G, Facciorusso A, Muscatiello N, Triantafyllou K. Meta-analysis indicates that add-on devices and new endoscopes reduce colonoscopy adenoma miss rate. *Eur J Gastroenterol Hepatol* 2018) is a previous meta-analysis from our group on the impact of distal attachments and new technologies on adenoma miss rate (AMR) and it is used in the Introduction section to present the available data on these devices utility. In any case, we down tuned our contribution in the introduction section by removing from the reference list one of our review papers discussing both add-on devices and new technologies (*ref. 7, highlighted yellow and strikethrough in the revised manuscript*). Finally, all authors have no conflict of interest regarding this study as clearly stated (*Page 2, revised manuscript*) and signed in the respective COI document.

6. The authors concluded :<<Use of the Endocuff during routine colonoscopy examination improves adenoma detection>> However this conclusion is true for operators with low-to moderate ADRs and not to all operators especially to operators with high ADRs. For the latter operators the use of endocuff might be costly and complicated.

Authors' response: We agree with the reviewer's comment. Moreover, we already emphasized on the difference effect of Endocuff-assisted colonoscopy according to endoscopist's ADR in the Discussion of the initial manuscript (*4th paragraph, highlighted yellow*) and further enriched it by incorporating reviewer's skepticism

(Discussion Section of the revised manuscript, last sentence of 4th paragraph, highlighted yellow).

7. In the title the question <<Does Endocuff use increase adenoma detection rate?>> predisposes the conclusion beforehand. For neutrality and objectivity of the study question should be avoided at the title.

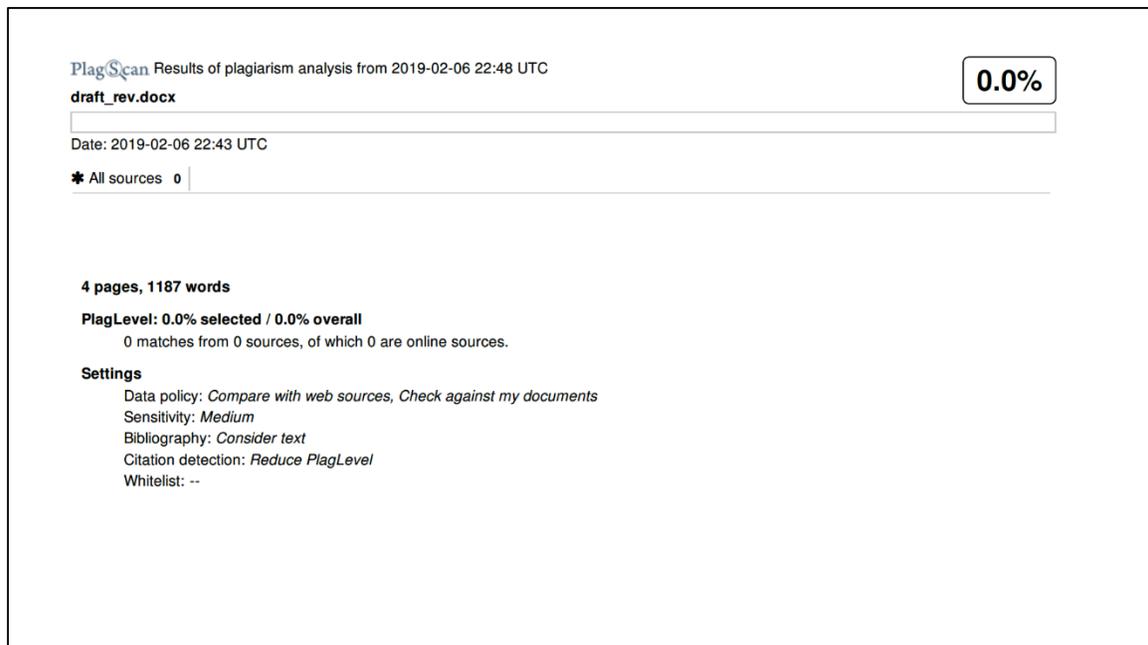
Authors' response: We thank the reviewer for this insightful comment. We have amended the title of our manuscript to "Effect of Endocuff use on colonoscopy outcomes: a systematic review and meta-analysis". In our opinion the revised title accurately reflects the study's main finding.

8. Another issue is the quality of colonoscopic preparation eg Boston Bowel Prep Scale (BBRS) score and endocuff use. Are there any studies? No such information are included in this study.

Authors' response: We are thankful to the reviewer for the valuable remark. All but one of the included studies reported on the scale used to evaluate the bowel preparation quality of participants. However, no study detected a difference between EAC and CC group in the quality of bowel preparation. Following reviewer's suggestion, we amended our manuscript (*Results section of the revised manuscript, Characteristics of studies included and Table 1*) to provide all available information to the readership.

9. There is plagiarism in the discussion. The authors in page 15 discussed a recently network meta-analysis of other than Endocuff modalities that might improve ADR. Although this discussion is interesting has no relation to the issue.

Authors' response: To ensure that no plagiarism exists in the Discussion section of our manuscript, you may find attached the result of the quality control process, where 0% of plagiarism was detected. Moreover, the Editorial cross check review of the original submission, available in the submission platform, did not detect plagiarism.



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Regarding the second comment we have modified the discussion accordingly by omitting the aforementioned paragraph (and the respective reference) (*Discussion, page 18, highlighted yellow and strikethrough*).

Reviewer No: 00070280

Reviewer's comment: This is a good study on an important topic. This can be accepted.

Authors' response: We thank the reviewer for this polite comment.