Manuscript NO: 59367
Title: EVALUATION OF AN EDUCATIONAL TELEPHONE INTERVENTION STRATEGY TO IMPROVE NON-SCREENING COLONOSCOPY ATTENDANCE. A RANDOMIZED CONTROLLED TRIAL

Dear Editor and Reviewers

On behalf of the authors I want to thank you for your kind letter of November 3er. The suggestions and criticisms of the Editorial Board and Reviewers were very helpful, and they will surely help to improve the quality of the manuscript. I believe we have answered them appropriately.

We revised our manuscript according to the BPG formatting guidelines for Randomized Controlled Trial and the "article highlight" section were added at the end of the main text. Changes to the manuscript have been reviewed by a native-English speaker. All authors have read the manuscript and conflict of interest statement, and approved their submission for publication.

We have included the page numbers in the revised manuscript to help the reviewers identify our changes.

We believe that this manuscript will be of a great interest to the readers of your Journal and we hope that the editorial board will appreciate our work and accepts our revised manuscript for publication in World Journal of Gastroenterology.

We look forward to hearing from you.

Yours faithfully

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RESPONSE TO EDITORS AND REVIEWER COMMENTS

Science editor:

1) The exclusion criteria do not exclude patients who had prior total or subtotal colectomy. These patients may not need bowel prep and may not need sedation. Please clarify the inclusion and exclusion criteria.

Response:

As stated in the study population and treatment allocation section, the inclusion criteria were of all consecutive outpatients referred for colonoscopy from November 2017 to May 2018 from the primary care centres in our health area. We did not exclude patients who had prior total or subtotal colectomy and any other condition that affected bowel prep or sedation, because the main objective of our study was to evaluate the attendance rate. Preparation or sedation were secondary objectives in our study and excluding these patients would imply a selection bias.

Following the Editor's suggestion, the inclusion and exclusion criteria has been clarified. *Material and methods. Study population and treatment allocation (page 7)*

2) The questions raised by the reviewers should be answered

Response:

The questions raised by the reviewers are answered below.

Reviewer #1:

The article "Evaluation of an educational telephone intervention strategy to improve non-screening colonoscopy attendance. A randomized controlled trial" has some troubles:

1) ABSTRACT - The Aim has more than 20 words.

Response:

The word "nurse" has been deleted in AIM to not use more than 20 words in the section. *Abstract. Aim (page 3)*

2) RESULTS - The author says "a total of 1485 patients (738 in the IG and 747 in the CG) were finally enrolled", but in the patient flow chart and all other tables, it is shown that 746 patients were enrolled in the control group and a total of 1484 patients.

Response:

The transcription error in the RESULTS section, which states that 747 patients have been included in the CG, has been corrected (746 patients have been really included). *Results. Patient characteristics (page 12)*

3) In the sub-analysis "Cleansing adequacy", the author says "a total of 627 and 673 colonoscopies (584 in patients contacted) were finally performed in the CG and IG, respectively". However, Table 5 shows that 674 patients in the IG and 634 patients in the CG performed colonoscopy.

Response:

Tables 5 and 6 of the study have been eliminated for publication, so the transcription error disappears. See explanation in points 5 and 6.

4) In the sub-analysis of patients' satisfaction, the author says "The information was rated as excellent in 49.4% (CG) and 26% (IG) of patients, P = <0.001", but in Table 4, it is informed the opposite: 49.4% in IG and 26% in CG.

Response:

The transcription error in the satisfaction section of the manuscript has been corrected. Table 4 is correct. *Results. Satisfaction (page 13)*

5) There are too many and too large tables.

Response:

Too many tables: We totally agree with the reviewer. Sometimes providing more data does not result in more information but in more confusion. Giving such prominence to colon cleansing data diverts attention from the primary objective of the study, which is attendance.

Therefore, following the reviewer recommendation, we have eliminated *Table 5 and Table 6* from the results of the study.

Large tables: To reduce the size of the tables we have eliminated redundant variables that did not provide special information to the study, such as PREVIOUS ENDOSCOPY (number) and LAST COLONOSCOPY (years).

Changes in Table 1 and Table 2.

6) DISCUSSION - The author says this is the first RCT of this subject in "non-screening colonoscopies", but it doesn't seem that this differentiation makes any sense. The indications of colonoscopy in this study were surveillance, diagnostic, or familiar screening. Familiar screening and surveillance may also be cancer screening.

Response:

The motivation of the study has been from the beginning to prove that ALL colonoscopies benefit from a previous educational intervention concerning attendance, and not only those of the screening.

In general, population screening programs have received more attention and interventions aimed to increase the quality standards, like attendance and many others. Most of those improvements have not been widely implemented to non-screening colonoscopies, including family history of CRC and surveillance colonoscopy.

We think it is a mistake that attendance is not a key quality parameter for ALL colonoscopies. If the patient does not attend, all other quality parameters are of no interest. The motivation and main objective of the study has been precisely

to try to give a wake-up call to change this attitude, so widespread in daily clinical practice.
To highlight this concepts we have added several comments in the manuscript. *Changes in Abstract. Background, and Introduction.*
NOTE: in the tables we have changed the term "Familiar screening" to "Family history of colorectal cancer" as it is more appropriate. *Changes in Table 1 and Table 2*.

7) There are also other studies demonstrating that contacting patients before colonoscopy can improve the quality of bowel preparation (PMID: 23503044, 26182387).
Response:
The reviewer is right that there are publications of educational interventions to contact patients to improve bowel cleansing. However, no study has focused the interest on improving attendance. In our study bowel cleansing was a secondary objective.
As explained in point 5, it has been decided to eliminate the tables related to colon cleansing to avoid confusion with the main objective of assessing the attendance.

8) Therefore, it doesn't seem that this study brings innovative information.
Response:
We do not agree with that comment. On the contrary we have showed that our educational measure of telephoning all patients with a colonoscopy appointment improves attendance, protocol compliance and patient satisfaction in the non-screening colonoscopy setting and has a large economic impact. Our study is also innovative because previous studies have focused the attention on population screening programs or bowel cleansing quality.

Reviewer #2:

The authors conducted a randomized controlled trial in a single tertiary center. They evaluated the impact of educational telephone call by a nurse on the colonoscopy appointment attendance for non-screening colonoscopies. The primary outcome was the non-attendance rate and the secondary outcomes included cost analysis, colonoscopy prep adequacy, and patient satisfaction. The authors also performed bivariate and multivariate analysis to identify the factors related to non-attendance. The study concept is important and the intervention is a practical solution. However, I have the following concerns regarding the study design and statistical analysis.

Major comments

1) The exclusion criteria do not exclude patients who had prior total or subtotal colectomy. These patients may not need bowel prep and may not need sedation. Please clarify the inclusion and exclusion criteria.

Response:

The inclusion criteria were of all consecutive outpatients referred for colonoscopy from November 2017 to May 2018 from the primary care centres in our health area. We did not exclude patients who had prior total or subtotal colectomy and any other condition that affected bowel cleansing or sedation, because the main objective of our study was to evaluate the attendance rate. Preparation or sedation were secondary objectives in our study and excluding these patients would imply a selection bias.

Following the Reviewer's suggestion, the inclusion and exclusion criteria has been clarified in the manuscript. *Material and methods. Study population and treatment allocation (pages 6-7)*

2) The authors mentioned that they contacted all patients by phone and patients provided verbal consent and later they provided a signed consent. How did you obtain a signed consent from patients who did not show up to their colonoscopy appointment?

Response:

All patients who did not show up were later contacted to request their signed consent, which was subsequently delivered by hand or by mail. This specification has been added to the manuscript. Material and methods. *Study population and treatment allocation (page 7)*

3) How did you evaluate the compliance with cleansing protocols? Did you ask patients to fill a survey? Please provide more details about the questionnaire. Was this questionnaire validated in previous studies?

Response:

Patients did not fill in any validated questionnaire. There was a face to face interview conducted by an endoscopy nurse at the colonoscopy appointment, before the colonoscopy, which included simple, short, and easy-to-understand questions regarding a) correct diet, b) split dose intake of the laxative, c) total intake of the laxative, and d) correct timing of the laxative. According to the predominant social-economic low class of our patients, we believe that a face-to-face interview is more accurate than a written survey to measure compliance with the bowel cleansing.

The responses were electronically recorded in clinical history of the patient for later review.

We have added this information in the manuscript. *Material and methods. Outcome measures (page 9). Data collection (page 10)*

4) The authors used the BBPS to report the adequacy of colonoscopy prep. Please clarify the cutoffs for adequacy based on the BBPS.

Response:

The BBPS cutoffs have been specified in the manuscript now. *Material and methods. Outcome measures (page 9).*

5) Why did you choose 13.9% and 8.9% to calculate the sample size? Are they based on prior studies? Please clarify.

Response:

Because there are scarce data for non-attendance rates in non-screening colonoscopy, to calculate the sample size we retrospectively obtained our non-attendance rate figures (non-published data) from November 2016 to May 2017, the same period of the study one year before.

This has been specified in the manuscript. *Material and methods. Statistical analysis (page11).*

6) The authors mentioned in the statistical analysis that they reported the qualitative variables were reported as frequency. What qualitative variables are you referring to? The study seems quantitative and not qualitative.

Response:

To better clarify the concept, regarding this kind of variables, we have changed the term qualitative by categorical.

7) How did you choose the variables included in multivariable analysis? Please clarify in the methods.

Response:

A backward stepwise criterion was used to variable selection for multivariate analysis. A p value of > 0.1 as removal criteria and <0.05 for inclusion criteria. Following this criterion, results from table 3 have slightly changed.

We have specified this analysis method in the manuscript. *Material and methods. Statistical analysis (page 11). Changes in Table 3.*

8) How did you consent participants before randomization? Please clarify the process.

Response:

We performed a prerandomization (Zelen's method) with a complete-double-consent design. This is a design previously described in the literature for RCT and published in cases when the intervention is an educational programme like ours. In this method informed consent is sought in the experimental group and in the reference group after randomization, mentioning the use of the other comparison group. Non-consenting patients are totally excluded from the study.

The postrandomized method would be methodologically incorrect in our study. We chose the prerandomized method to avoid the significant selection bias that would have been created by contact with the patient prior to randomization in a study where assessing the applicability of contact is crucial. The risk of not participate or drop out would also have been high since a very attractive intervention for the patient is valued, generating new bias. A minor criterion for choosing this randomization method was to enhance recruitment.

The randomization method used is clear in the flow chart but confusing in the text. Following the Reviewer's suggestion, we have clarified the process of

patient consent in the text. *Material and methods. Study population and treatment allocation (page 7).*

9) The cost analysis section in the results is unclear. The methods of calculation are not well-defined. I recommend using number of patients instead of rates because the cost of the procedure is linked to each patient regardless of the rates. I did not find the cost analysis easy to understand and it was confusing. Please clarify this section and how did you end up with the final number (€56547).

Response:

The text of the cost analysis section has been modified, according to the reviewer's recommendations, calculating cost per number of patients and clearly specifying the procedure performed to calculate the benefit per patient and the annual benefit of the educational intervention. *Results. Cost analysis (pages 12-13).*

Note that the final figure changes slightly when changing the calculation method, observing a final profit figure of € 55 600.

10) The authors reported this consideration "if we consider a broader definition of bowel preparation failure, including not only inadequate bowel cleansing but also non-attendance and non-compliance with patient preparedness protocols." This definition is not an acceptable definition for inadequate prep and should not be reported. Considering patients who did not attend as inadequate prep does not seem appropriate.

Response:

The definition and data regarding the expanded definition of colon cleansing failure have been removed, following the reviewer's recommendations. *Results. Cleansing adequacy (page 13)*

11) What does receiving allocated intervention mean in the flow chart? How is it possible that CG received an intervention?

Response:

Patients in the CG did not receive any allocated intervention. There are sections in the Flow Chart that are confusing and have been modified. Specifically, as regards the reviewer's doubt on this point, the term "allocated intervention" has been removed. *Changes in Figure 1.*

12) Table 5 and 6. The intervention showed no significance in the bivariable analysis, why did you include it in the multivariable analysis? I do not think it is appropriate statistically to do so. I recommend removing both tables.

Response:

Sometimes providing more data does not result in more information but in more confusion. Giving such prominence to colon prep data diverts attention from the primary objective of the study, which is attendance.

Following Reviewer´s suggestions Table 5 and Table 6 have been removed.

13) Table 3- why did not you include abdominal/pelvic surgery in the multivariate analysis although it was significant in the bivariate analysis? Please clarify. Also, waiting time was not significant in the bivariate but it was used in the multivariate. Please clarify the methods of multivariate analysis.
Response:
This question has already been answered in the point number 7 of mayor comments. *Materials and methods. Statistical analysis (page 11). Changes in Table 3.*

Minor comments

1) Please spell out all abbreviations before using them "Consenting participants were randomized to the CG and the IG 10 days before the colonoscopy appointment" Also these groups should be defined before using these terms. Similarly, ITT, PP.
Response:
Errors in the manuscript regarding the use of abbreviations have been solved, for IG / CG: *Material and methods. Study population (page 7)*, and for ITT / PP: *Material and methods. Statistical analysis (page 11).*

2) Table 1 – what does this term mean "Familiar screening"?
Response:
The term "Familiar screening" is incorrect. The correct term is "Family history of colorectal cancer (CRC)" and we have changed this in the tables. The term "Family history of CRC" is widely used and we think it is not necessary to be defined in the text. *Changes in Table 1 and Table 2.*

3) Table 3 – the 95% CI of age crossed 1 (0.97-9.99) however P was 0.001. please clarify if these numbers are accurate.
Response:
We have corrected the transcription error in Table 3 in relation to the 95% CI (9.99 is actually 0.99). *Changes in Table 3.*

4) I recommend reporting P value as "<0.001" instead of 0.000
Response:
We have corrected the format of the numbers. *Changes in Table 3.*

5) Waiting time to endoscopy, you report OR as 1.0 and P value is under 0.05. Please clarify the numbers.
Response:
According to the method used to choose the variables of the multivariate analysis this variable has been eliminated (see point 7 in mayor comments). *Changes in Table 3.*

6) Abstract: results section. The authors reported the rates of non-attendance however they reported OR and 95% CI. The rates should be compared and P

value should be provided. Reporting OR is not consistent with comparing proportions.

Response:

We have changed the Abstract to provide the P and not the OR when comparing proportions. *Abstract. Results (pages 3-4).*

7) Abstract: results section. I recommend reporting the number of patients who participated in the study and not the number of patients randomized. Because randomization occurred before obtaining consent and intervention.

Response:

Following the Reviewer´s suggestion we have reported the number of patients who participated in the study. *Abstract. Results (page 3).*

8) Methods – statistical analysis. Please correct this "Student's-test" to "Student's t-test"

Response:

We have corrected Student´s t-test. *Materials and methods. Statistical analysis (page 11).*

9) Please clarify the method to select variables for the multivariate logistic regression. What method did you use and why?

Response:

This question has already been answered in the point number 7 of mayor comments. *Materials and methods. Statistical analysis (page 11). Changes in Table 3.*

10) The authors reported that there are 747 patients in the CG, however in Figure1 and Table 1 they reported 746. Please clarify the numbers.

Response:

The transcription error in the RESULTS section, which states that 747 patients have been included in the CG, has been corrected (746 patients have been really included). *Results. Patient characteristics (page 12)*

11) Figure 1 – what do you mean by lost to follow up? How was that defined?

Response:

Patients did not receive any follow up. There are sections in the Flow Chart that are confusing and have been modified. Specifically, as regards the reviewer's doubt on this point, the term "lost to follow up" has been removed. *Changes in Figure 1.*

12) Table 2 – you reported "abdominal/pelvic" I think you meant to add surgery. Please correct it.

Response:

The transcription error in table 2 has been corrected, adding the word "surgery". *Changes in Table 2.*

13) Table 2 – previous endoscopy number. The SD is larger than the mean in that row which means that the variable is not normally distributed. How is it

possible that P value was statistically significant while the range of mean (SD) is very wide? Similarly, last colonoscopy row.

Response:

Both variables have been eliminated from the study for not providing relevant information and causing statistical problems. *Changes in Table 1 and Table 2.*

14) Table 4 – please correct the word "regime" to "regimen"

Response:

The transcription error with the word "regimen" in table 4 has been corrected. *Changes in Table 4.*

15) Table 4 – what do you mean by the word "media"? You should report the mean with SD, not median.

Response:

The transcription error with the word "mean" in table 4 has been corrected. *Changes in Table 4.*

16) The authors reported "it also did not reach significance in the PP analysis, IG PP 93.2% (P = 0.08)]." Please provide the comparison between 2 rates and report the P value for this comparison.

Response:

The text in the CLEANSING ADEQUACY section has been modified to correctly relate the comparison between 2 rates and the *P*-value. *Results. Cleansing adequacy (page 13).*

17) The authors reported "The information was rated as excellent in 49.4% (CG) and 26% (IG) of patients" I think these numbers are mixed based on the table 4. Please clarify.

Response:

The transcription error in the satisfaction section has been corrected. Table 4 is correct. *Results. Satisfaction (page 13).*