

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	bmjopen-2020-044308.R1 Assessment of adherence to oral nutritional supplementation and exploration of barriers and facilitators in patients after gastric cancer surgery: A mixed methods study protocol
AUTHORS	Wan, Guang-ying; Xue, Hui; Yuan, Hua; Wang, Xin; Li, Hui-qin; Zhang, Xiuying

VERSION 1 – REVIEW

REVIEWER	Arved Weimann Dept. of General and Visceral Surgery Hospital St. George Leipzig Germany
REVIEW RETURNED	29-Nov-2020

GENERAL COMMENTS	<p>The compliance of patients after gastrectomy regarding the intake of oral nutritional supplements is often limited for many reasons. Therefore, the study protocol focusing on the exploration of barriers and facilitators is a matter of clinical relevance.</p> <p>p. 4 line 48 - Major criticism are the nutritional indicators. Serum albumin is not considered to be appropriate. Body composition analysis and or functional parameters like hand grip strength or 6-min walking distance should be considered.</p> <p>p. 5 line 10 – This exploration should be clarified Clear definition of compliance and adherence is recommended. The Chinese policy to reimburse ONS for only for one week may lead to a selection bias for the inclusion of patients for 12 weeks if the patients have to buy the ONS on their own. Another bias may be the motivation of the patient by the physician prescribing ONS. The authors may also refer to the ESPEN guidelines for surgical patients giving the recommendation for enteral nutrition via a jejunostomy after gastrectomy. With special regard to the qualitative study and the interview outline the input of a psychologist and/or social scientist is suggested.</p> <p>Minor: p.3 line 12 – reduced overall survival p. 3 line 51 – ESPEN</p>
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REVIEWER	Joanna Colleen Dionne McMaster University
REVIEW RETURNED	01-Dec-2020

<p>GENERAL COMMENTS</p>	<p>Thank you for the opportunity to review this interesting protocol that addresses an important knowledge gap in the nutritional care of gastric cancer patients. Below I have included my comments on the protocol. Best of luck with your research.</p> <p>Comments-</p> <p>Abstract-</p> <p>methods and analysis- add in "mixed methods" research methodology...</p> <p>12w-is this 12 week longitudinal study? If so, use 12 weeks.</p> <p>primary endpoints- should say include...followed by list of end points.</p> <p>comment- is the study powered for all these primary endpoints? Or just one. Suggest primary endpoint- (list 1), followed by secondary and tertiary.</p> <p>Line 47- suggest rewording the last sentence to enhance clarity.</p> <p>Suggest- The qualitative study will be informed by a convenience sample of patients from the qualitative study. The interview guide will be informed by the quantitative study.</p> <p>Introduction-</p> <p>first sentence- suggest rewording - third highest cause of cancer deaths in the world, accounting for 841,000 deaths in 2013.</p> <p>page 2, line 54- change to dramatic weight loss from dramatically....</p> <p>page 3, line 33- suggest wording, the compliance with ONS is unsatisfactory, with rates as low as 42%.</p> <p>Objectives- clearly outlined.</p> <p>Study design</p> <p>page 5- suggest adding in "mixed methods" methodology with an explanatory...</p> <p>Patient and public involvement</p> <p>page 5- grammatical error, just rewording for clarity.</p> <p>Quantitative study</p> <p>page 5- as in the abstract, suggest if 12 week longitudinal study suggest spelling out the whole word</p> <p>page 6- suggest last sentence be reworded for clarity.</p> <p>Inclusion and Exclusion criteria</p> <ul style="list-style-type: none"> - Any plan on stratification of stages of cancer or type of surgery. Would think that those with stage three cancer with a gastrectomy would be different from stage I/II who had a distal gastrectomy in terms of nutritional status and outcomes? <p>Methodology- outcomes appropriate</p> <ul style="list-style-type: none"> - suggest using interview guide rather than interview outline - suggest adding in open "ended" questions in data collection section 4.2.3 <p>-Page 13 line 12 missing close of quotations.</p> <p>Strengths and Limitations</p> <p>The authors highlight strengths of the study, but do not list limitations of the study. Suggest expanding on the limitations of the study.</p>
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VERSION 1 – AUTHOR RESPONSE

REVIEWER COMMENTS

Reviewer: 1

Dr. Arved Weimann, Klinikum St. Georg gGmbH

Comments to the Author:

The compliance of patients after gastrectomy regarding the intake of oral nutritional supplements is often limited for many reasons. Therefore, the study protocol focusing on the exploration of barriers and facilitators is a matter of clinical relevance.

Response: Thank you very much for your recognition of our study and every comment you put forward. For each comment, we carefully considered and made detailed adjustments to improve the quality of this study. In order to improve the quality of the manuscript, we have edited and revised the manuscript through professional company. (<https://www.aje.com/>).

1. p. 4 line 48- Major criticism are the nutritional indicators. Serum albumin is not considered to be appropriate. Body composition analysis and or functional parameters like hand grip strength or 6-min walking distance should be considered.

Response: Thank you very much for your patient review and suggestions. After referring to your opinion, we found that serum albumin has a half-life of 20 days, which is a poor nutritional indicator¹. Therefore, we decided to cancel albumin as the outcome indicator of our study. By referring to relevant study, we found that grip strength is a necessary indicator for diagnosing sarcopenia in patients with gastric cancer, and can predict the survival and complications of patients after radical^{2,3}. Therefore, we decided to select grip strength as the outcome indicator of this study, which will measure at baseline and 12 weeks after surgery. We have made changes in tables and the full text. (It has been marked in red.)

2. p. 5 line 10 – This exploration should be clarified

Response: Thanks very much for your comments. It is our language error that caused your misunderstanding, I am very sorry for that. The “exploration” should mean “explain”. In the mixed-method with an explanatory sequential approach, the first purpose of qualitative research is to

explain quantitative research.¹³ So, we change “Exploration of the gastric cancer patients’ views about barriers, facilitators, based on the results of quantitative studies.” to: “Further explain factors that promote and hinder gastric cancer patient adherence to ONS in the quantitative study.” (Please see P7 Line28-31, it has been marked in red.)

3. Clear definition of compliance and adherence is recommended.

Response: Thanks very much for your comments. We reviewed the literature about “compliance” and “adherence” have found the definition of two terms. “Compliance: patients’ obedience to recommendations with prescribed treatments”⁴; “Adherence : Voluntary cooperation of the patient in taking drugs or medicine as prescribed. This includes timing, dosage, and frequency.”¹⁴ “ Adherence: the extent [to] which a person’s behavior taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”⁵. In our protocol, indicators for measuring patient's adherence with ONS include time and dose, so the expression “adherence” is more appropriate. We have made changed “compliance” as “adherence” in the manuscript. (It has been marked in red in the manuscript.) And added the definition of adherence in the manuscript. (Please see P13 Line4-7, it has been marked in red.)

4. The Chinese policy to reimburse ONS for only for one week may lead to a selection bias for the inclusion of patients for 12 weeks if the patients have to buy the ONS on their own.

Response: Thanks very much for your comments. The suggestion you mentioned is indeed a limitation of the design of this protocol, but the Chinese policy has not changed so far. In previous studies on ONS in other countries, ONS preparations taken by patients can be obtained for free^{16,17}, but in our study is need patients to purchase some ONS products by themselves. Regardless of whether the patient has purchased enough ONS for 12 weeks, we will include the results in the analysis. However, due to the different economic conditions of each patient, when patients are included, selection bias will occur, which will affect the final level of adherence. If the economic factor in the final result is a factor that affects patients' taking ONS, we will discuss it. We have written it into the limitations of this protocol. (Please see P3-P4, ‘Strengths and limitations’ section fourth point, it has been marked in red.)

5. Another bias may be the motivation of the patient by the physician prescribing ONS.

Response: Thanks very much for your comments. The suggestion you mentioned is indeed a limitation of the design of this protocol. In our study, the physician will be prescribing the ONS for 2 weeks. After discharge from the hospital, all patients purchased it by themselves until 12 weeks after the operation. This may lead to information bias, leading to higher patient adherence in the first two weeks than in other time periods. We have written it into the limitations of this protocol. (Please see P3-P4, 'Strengths and limitations' section fifth point, it has been marked in red.)

6. The authors may also refer to the ESPEN guidelines for surgical patients giving the recommendation for enteral nutrition via a jejunostomy after gastrectomy.

Response: Thanks very much for your comments. Enteral nutrition via a jejunostomy after gastrectomy is indeed an effective way to improve the nutritional status of patients. But in the context of Enhanced recovery after surgery (ERAS), ONS is the first choice for enteral nutrition, which is in line with the concept of early oral feeding of ERAS^{6, 7}. Studies have shown that giving patients ONS after discharge can increase their nutrition and energy intake, effectively promote wound healing, increase body mass, reduce complications, reduce hospital readmission rates, improve quality of life, and save social and medical costs^{8,9}. And the adherence of ONS is currently a hot topic, so we pay more attention to the adherence of ONS.

7. With special regard to the qualitative study and the interview outline the input of a psychologist and/or social scientist is suggested.

Response: Thank you very much for such valuable comments, which will be of great help to the rigor of this study design and future data analysis. During the formation of the interview outline and the process of qualitative data analysis, the suggestions of psychologists are very important. With the help of a psychologist, we can obtain more effective information in the interview process and form more professional codes and topics in data analysis. Therefore, we will refer to the suggestions of psychologists when designing the interview outline and analysing the qualitative data. We have added relevant statements in the manuscript. (Please see P14 Line53-59, and P16 Line 43-48, "Validity and reliability/rigor" section, it has been marked in red.)

8. p.3 line 12 – reduced overall survival

Response: Thanks very much for your comments. It is our expression error that caused your inconvenience, we have made changed “reduce overall survival” as “reduced overall survival” in the manuscript. (Please see P4 Line53, it has been marked in red.)

9. p. 3 line 51 – ESPEN

Response: Thanks very much for your patient and meticulous comments. It is our spelling error that caused your inconvenience, I am very sorry for that. We have made changed “EPSEN” as “ESPEN” in the manuscript. (Please see P5 Line 38, it has been marked in red.)

Reviewer: 2

Thank you for the opportunity to review this interesting protocol that addresses an important knowledge gap in the nutritional care of gastric cancer patients. Below I have included my comments on the protocol. Best of luck with your research.

Response: Thank you very much for your patient review and suggestions, we have made serious amendments in accordance with your comments. We have edited and revised the manuscript through professional company. (<https://www.aje.com/>).

Comments-

Abstract-

1. methods and analysis- add in "mixed methods" research methodology...

Response: Thank you very much for your patient review and suggestions. We have added relevant statements in the manuscript. (Please see P2 Line35- P3 Line4, it has been marked in red.)

2. 12w-is this 12 week longitudinal study? If so, use 12 weeks.

Response: Thanks very much for your comments. We want to express is 12-week longitudinal study, we have changed “12w” to “12 weeks” in the manuscript. (Please see P2-Line38, “Abstract-Methods and analysis” section, it has been marked in red.)

3. primary endpoints- should say include...followed by list of end points.

comment- is the study powered for all these primary endpoints? Or just one. Suggest primary endpoint- (list 1), followed by secondary and tertiary.

Response: Thanks very much for your comments. We have changed “the primary endpoints including patients' compliance with oral nutritional supplements, weight, body mass index and serum albumin. The 30-day readmission rate, complications, and adverse reactions will be collected as secondary endpoints.” to “The primary endpoints include patient adherence to oral nutritional supplements, weight, body mass index and grip strength followed by 30-day readmission rate, complications, and adverse reactions.” in the manuscript. (Please see P2-Line 46-54, “Abstract- Methods and analysis” section, it has been marked in red.) The authors agree that according to your suggestions, our research content can be explained more clearly, so we have adjusted the table2 in the main text accordingly. (Please see Table 2, it has been marked in red.)

4. Line 47- suggest rewording the last sentence to enhance clarity. Suggest- The qualitative study will be informed by a convenience sample of patients from the qualitative study. The interview guide will be informed by the quantitate study.

Response: Thanks very much for your comments. we have changed “To provide in-depth insight into the quantitative results, we will select the samples and design the interview outline of the qualitative study based on the results of the quantitative study.” to “The qualitative study will be informed by a purposive sample of patients from the quantitative study, the interview guide will be informed by the quantitative study, and in-depth insight will be provided into the quantitative results.” in the manuscript. (Please see P8 Line 4-12, it has been marked in red.)

Introduction-

1. first sentence- suggest rewording - third highest cause of cancer deaths in the world, accounting for 841,000 deaths in 2013.

Response: Thanks very much for your comments. We have made changed “the third highest cause of cancer death in the world, gastric cancer killed approximately 841,000 people in 2013” as “the third most common cause of cancer-related deaths in the world, gastric cancer accounted for 841,000 deaths in 2013”in the manuscript. (Please see P4 Line30-33, it has been marked in red.)

2. page 2, line 54- change to dramatic weight loss from dramatically....

Response: Thanks very much for your comments. We have made changed “leads to dramatically weight loss” as “leading to dramatic weight loss” in the manuscript. (Please see P4 Line38-40, it has been marked in red.)

3. page 3, line 33- suggest wording, the compliance with ONS is unsatisfactory, with rates as low as 42%.

Response: Thanks very much for your comments. We have made changed “However, the compliance with ONS is unsatisfactory, the compliance rate even as low as 42%” as “However, adherence to ONS is unsatisfactory, with rates as low as 42%” in the manuscript. (Please see P5 Line20, it has been marked in red.)

Objectives- clearly outlined.

Response: Thanks very much for your comments. We have added relevant statements in the manuscript. (Please see P6-7, “AIMS, OBJECTIVES AND RESEARCH QUESTIONS” section, it has been marked in red.)

Study design

page 5- suggest adding in "mixed methods" methodology with an explanatory...

Response: Thanks very much for your comments. We have added relevant statements in the manuscript. (Please see P7 , “Study design” section, it has been marked in red.)

Patient and public involvement

page 5- grammatical error, just rewording for clarity.

Response: Thank you for your comments. We are very sorry for the trouble caused by our language error. We have changed the relevant expressions in the manuscript. We have edited and revised the manuscript through professional company. (<https://www.aje.com/>). (Please see P8 Line25-28, “Patient and public involvement” section , it has been marked in red.)

Quantitative study

1. page 5- as in the abstract, suggest if 12 week longitudinal study suggest spelling out the whole word

Response: Thank you for your comments. We have made changed “12 w” as “12 week” in the manuscript. (Please see P8 Line33, it has been marked in red.)

2. page 6- suggest last sentence be reworded for clarity.

Response: Thank you for your comments. We have reworded this sentence. We have edited and revised the manuscript through professional company. (<https://www.aje.com/>). (Please see P8 Line56- P9Line17, it has been marked in red.)

Inclusion and Exclusion criteria

1. Any plan on stratification of stages of cancer or type of surgery. Would think that those with stage three cancer with a gastrectomy would be different from stage I/II who had a distal gastrectomy in terms of nutritional status and outcomes?

Response: Thank you for your comments. This is also the problem we encountered in the design process. We read the relevant study and found that the stages and surgical methods of gastric cancer are indeed related to the prognosis of patients^{11,12}, for example, surgical method of gastric cancer is an independent risk factors for mortality. But gastric cancer staging I-III is not a predictor of postoperative malnutrition¹⁰. Moreover, ONS for patients with total gastrectomy is more conducive to the prognosis¹⁷. At the same time, we also refer to other related studies on postoperative nutrition for gastric cancer, patients with stage I-III are used as the inclusion criteria^{18,19}. Therefore we included the corresponding sample. Taking into account the factors of cancer stages and surgical methods, when we do data statistics in the future, the corresponding data and outcome indicators will also be analyzed.

Methodology- outcomes appropriate

1. - suggest using interview guide rather than interview outline

Response: Thank you for your comments. We have changed “interview outline” to “interview guide” in the manuscript. (It has been marked in red.)

2. - suggest adding in open "ended" questions in data collection section 4.2.3

Response: Thank you for your comments. We have added “Finally, we will encourage patients to make suggestions to improve adherence to ONS. For example, “Do you have any suggestions?” and “Anything else you’d like to add that we haven’t covered?” in the manuscript. (Please see P15 Line 30-36, it has been marked in red.)

3. -Page 13 line 12 missing close of quotations.

Response: Thank you for your comments. We have added a quotation in the manuscript. (Please see P15 Line41, it has been marked in red.)

Strengths and Limitations

The authors highlight strengths of the study, but do not list limitations of the study. Suggest expanding on the limitations of the study.

Response: Thank you for your comments. We have added “Limitation” at “Strengths and limitations” section of our manuscript (after the abstract). (Please see P3-P4 ‘Strengths and limitations’ section, it has been marked in red.)

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4. Bissonnette JM. Adherence: a concept analysis. *J Adv Nurs* 2008;63(6):634-43. doi: 10.1111/j.1365-2648.2008.04745.x [published Online First: 2008/09/24]
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 11. Wang S, Xu L, Wang Q, et al. Postoperative complications and prognosis after radical gastrectomy for gastric cancer: a systematic review and meta-analysis of observational studies. *World J Surg Oncol* 2019;17(1):52. doi: 10.1186/s12957-019-1593-9 [published Online First: 2019/03/20]
 12. Fang Y, Wu C, Gu X, et al. Perioperative mortality and morbidity prediction using POSSUM, P-POSSUM and APACHE II in Chinese gastric cancer patients: surgical method is a key independent factor affecting prognosis. *Int J Clin Oncol* 2014;19(1):74-80. doi: 10.1007/s10147-013-0525-x [published Online First: 2013/03/12]
 13. Creswell, J. (2003). Research design: Qualitative, quantitative and mixed methods and approaches.
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 19. Shimizu N, Oki E, Tanizawa Y, et al. Effect of early oral feeding on length of hospital stay following gastrectomy for gastric cancer: a Japanese multicenter, randomized controlled trial. *Surg Today* 2018;48(9):865-74. doi: 10.1007/s00595-018-1665-4 [published Online First: 2018/05/04]