

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Disease knowledge, medical experience, health-related quality of life, and health-care costs among patients with advanced colorectal cancer in China: protocol for a nationwide multi-center survey
AUTHORS	Liu, Yin; Xu, Hui-fang; Zhang, Xi; Yu, Yan-qin; Zhao, Yuqian; Zhang, Shaokai; Qiao, Youlin

VERSION 1 – REVIEW

REVIEWER	Guo, Feng German Cancer Research Centre
REVIEW RETURNED	19-Sep-2021

GENERAL COMMENTS	<p>Liu et al planned a national, multi-center survey to investigate the knowledge, medical experience, health-related quality of life, and health-care costs among Chinese patients with advanced CRC. I enjoyed reading it, feel it is certainly a relevant topic given the large cancer burden. I do have a few questions and comments:</p> <p>What would be the age range of the study population? According to the sentence on Page 6, Line 14, the authors planned to enroll patients aged <18 years and require parental consent alongside. Apart from parental consent, would the parents also answer the questionnaires for their children? In addition, would the authors perform the analyses among the entire study population or among age-stratified populations?</p> <p>Given that family history of CRC might also have an impact on patients' knowledge of CRC prevention, the authors could consider adding family history in the 1st-degree family members to the self-report questionnaires (Page 7, lines 29-33).</p> <p>The authors asked for information on patients' screening history in the questionnaire; however, all of the questions were colonoscopy-related. Given that fecal tests, such as FITs, are more likely to be used and can also lead to a follow-up colonoscopy after positive results, the authors could consider adding questions on fecal tests in the questionnaire.</p>
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REVIEWER	Gurney, JK University of Otago, Department of Public Health
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	Review of BMJOpen-2021-054403 Thank you for the opportunity to review this protocol manuscript titled 'PROTOCOL: Introduction of the largest colorectal cancer
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	<p>survey in China: a nationwide multi-center study'. I have listed specific comments below.</p> <ul style="list-style-type: none"> • The whole manuscript would (understandably, given the researchers are China-based) benefit from editing by a native English speaker, to polish the English within the manuscript. For example, the first sentence of the Abstract should state 'Colorectal cancer (CRC) is one of the most common cancers in China.' Or in the Strengths and Limitations section of the Abstract, the word 'species' in the following sentence should be replaced with 'type' (or similar): 'The methodology of this study has good replicability and can be applied to the other cancer species.' • The authors mention several times that most first diagnoses of colorectal cancer in China are of advanced disease (e.g. 'Even worse, most CRC patients have developed to advanced stage at the time of their first diagnosis[9].'). It would be useful to know what proportion of CRC patients are diagnosed with advanced disease (i.e. we need more information than 'most CRC patients'). • The rationale for the inclusion of the cost/economic evaluation within the study needs to be improved – this is only mentioned briefly. Why was it necessary to look at this within the current (patient-focussed) study? • The sample size section of the Methods needs some clarification. What was the basis for including 1% of the eligible advanced CRC population in China? Is it reasonable to assume that 90% of patients who were asked to participate would do so (i.e. 10% non-response rate)? This seems high – what is the rationale for this? It is also difficult to follow Table 1, in terms of how the final sample size was decided upon – for example, how do we arrive at 347 participants in the Northern region, based on the information provided in Table 1? This needs clarification. • The cost estimation aspect of the project needs much further detail – how are costs of treatment going to be estimated? Do the researchers have access to costings of treatment? Is the costing going to be what the treatment costs the health care system, or the patient, or both? This needs to be clarified. • From my perspective, the statistical analysis is not appropriate for a cross-sectional study – since it involves analysis of changes in outcomes before and after CRC treatment (i.e. the pre-post treatment analysis suggested by the reviewers beneath the heading 'Comparative analysis'). If this is a cross-sectional survey, it would seem more appropriate to complete descriptive analysis that tells us the current state of the measured outcomes in China right now, with perhaps comparisons between regions to assess between-region variation (if this is useful).
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VERSION 1 – AUTHOR RESPONSE

Reviewe (s)' Comments

Reviewer: 1

Dr. Feng Guo, German Cancer Research Centre

Comments to the Author:

Liu et al planned a national, multi-center survey to investigate the knowledge, medical experience, health-related quality of life, and health-care costs among Chinese patients with advanced CRC. I enjoyed reading it, feel it is certainly a relevant topic given the large cancer burden. I do have a few questions and comments:br />

1. What would be the age range of the study population? According to the sentence on Page 6, Line 14, the authors planned to enroll patients aged <18 years and require parental consent alongside. Apart from parental consent, would the parents also answer the questionnaires for their children? In addition, would the authors perform the analyses among the entire study population or among age-stratified populations?

RE: Thanks for your suggestion. In fact, during the investigation, we found that there were very few CRC patients aged <18 years, and they could not answer questions such as disease knowledge and medical experience by themselves. Therefore, we revised the inclusion criteria, and only included CRC patients aged ≥ 18 years old (See Paragraph 2, Page 6). We will also do subgroup analyses according to gender, median age, region, disease stages and so on (See the last Paragraph, Page 11).

2. Given that family history of CRC might also have an impact on patients' knowledge of CRC prevention, the authors could consider adding family history in the 1st-degree family members to the self-report questionnaires (Page 7, lines 29-33).

RE: Thanks for your suggestion. We have added "A first-degree family history of colorectal cancer". For the collected questionnaires, we will separate this term from "Others" in statistical analysis.

3. The authors asked for information on patients' screening history in the questionnaire; however, all of the questions were colonoscopy-related. Given that fecal tests, such as FITs, are more likely to be used and can also lead to a follow-up colonoscopy after positive results, the authors could consider adding questions on fecal tests in the questionnaire.

RE: Thanks for your suggestion and sorry for the confusion we caused. In fact, information on patients' screening history we planned to collect includes: have the patients been screened, the methods (i.e. faecal immunological test (FIT), colonoscopy, sigmoidoscopy, et al) and frequency of screening. However, given that colonoscopy is the standard screening method with the highest performance, we only collect barriers against colonoscopy. We have revised the manuscript, please see Paragraph 4, Page 8.

Reviewer: 2

Dr. JK Gurney, University of Otago

Comments to the Author:

Review of BMJOpen-2021-054403

Thank you for the opportunity to review this protocol manuscript titled 'PROTOCOL: Introduction of the largest colorectal cancer survey in China: a nationwide multi-center study'. I have listed specific comments below.

1. The whole manuscript would (understandably, given the researchers are China-based) benefit from editing by a native English speaker, to polish the English within the manuscript. For example, the first sentence of the Abstract should state 'Colorectal cancer (CRC) is one of the most common cancers in China.' Or in the Strengths and Limitations section of the Abstract, the word 'species' in the following sentence should be replaced with 'type' (or similar): 'The methodology of this study has good replicability and can be applied to the other cancer species.'

RE: Thanks for your suggestion. We have revised and a native English-speaker has helped to complete a thorough proofread of the text and correct any spelling and grammar errors.

2. The authors mention several times that most first diagnoses of colorectal cancer in China are of advanced disease (e.g. 'Even worse, most CRC patients have developed to advanced stage at the

time of their first diagnosis[9].'). It would be useful to know what proportion of CRC patients are diagnosed with advanced disease (i.e. we need more information than 'most CRC patients').

RE: Thanks for your suggestion. We have added (Even worse, about 56% of CRC patients have developed advanced stage at diagnosis).

3. The rationale for the inclusion of the cost/economic evaluation within the study needs to be improved – this is only mentioned briefly. Why was it necessary to look at this within the current (patient-focussed) study?

RE: Thanks for your comments. We have explained the necessity of cost/economic evaluation in greater detail in Introduction section.

4. The sample size section of the Methods needs some clarification. What was the basis for including 1% of the eligible advanced CRC population in China? Is it reasonable to assume that 90% of patients who were asked to participate would do so (i.e. 10% non-response rate)? This seems high – what is the rationale for this? It is also difficult to follow Table 1, in terms of how the final sample size was decided upon – for example, how do we arrive at 347 participants in the Northern region, based on the information provided in Table 1? This needs clarification.

RE: Thanks for your comments. For a targeted population with large sample (more than 150,000), a sampling ratio of 1% is enough to ensure the representativeness of the sample (Reference 1). Therefore, it is designed that 1% (about 4,000) of the eligible advanced CRC patients in China are included.

In order to reduce selection bias, the non-response rate should be less 20% and the lower the better. In this study, we set the non-response rate as 10% according to the response rate of patients in the pilot survey.

We have added the explanation of the final sample size. Proportional allocation was used to determine the sample size of each region, according to the population density. For example, in Table 1, the proportion of population in Northeast China is 7.8% (10,836/139,606), therefore, the sample size in Northeast China is equal to 7.8% times 4,445, or 347.

Reference 1: Neuman W. Social Research Methods: Qualitative and Quantitative Approaches 2000.

5. The cost estimation aspect of the project needs much further detail – how are costs of treatment going to be estimated? Do the researchers have access to costings of treatment? Is the costing going to be what the treatment costs the health care system, or the patient, or both? This needs to be clarified.

RE: Thanks for your suggestion. We have revised and added Table 4 to present the details of the costs. The costs of CRC will be estimated from a societal perspective, including direct medical costs and direct non-medical costs. We will use an annual timeframe to retrospectively collect all costs since the time of diagnosis. The costs will be collected through medical records or patients' self-report if medical records are not available. (Please see Paragraph 1, Page 10)

6. From my perspective, the statistical analysis is not appropriate for a cross-sectional study – since it involves analysis of changes in outcomes before and after CRC treatment (i.e. the pre-post treatment analysis suggested by the reviewers beneath the heading 'Comparative analysis'). If this is a cross-sectional survey, it would seem more appropriate to complete descriptive analysis that tells us the current state of the measured outcomes in China right now, with perhaps comparisons between regions to assess between-region variation (if this is useful).

RE: Thanks for your suggestion. After carefully consideration, we agree this study is not entirely cross-sectional, given that patients' quality of life is collected at two time points. Therefore, we deleted "cross-sectional" and redefined the study design as "This is a nationwide, hospital-based, multi-center survey conducted in Mainland China." (See Study Design section, in Page 5).

Given that 'Comparative analysis' may be confusing, we deleted it. Descriptive analysis is the main method, but we also do subgroup and regression analyses to explore factors associated with CRC knowledge, colonoscopy screening, targeted agents, and the changes of HRQOL. Actually, subgroup and regression analyses are widely used both in cohort studies and cross-sectional studies, Such as Reference 2 and Reference 3.

Reference 2: Luxia Zhang, Fang Wang, Li Wang, et al; Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* (London, England) 2012 Mar 03;379(9818):815-22
doi:10.1016/S0140-6736(12)60033-6

Reference 3: William Encinosa, Amy J Davidoff; Changes in Antiemetic Overuse in Response to Choosing Wisely Recommendations. *JAMA oncology* 2017 Mar 01;3(3):320-326
doi:10.1001/jamaoncol.2016.2530