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Assessment of adherence to oral nutritional supplementation and exploration of barriers and facilitators in patients after gastric cancer surgery: a mixed methods study protocol

Guang-ying Wan,[1] Hui Xue,[2] Hua Yuan,[3] Xin Wang,[4] Hui-qin Li,[1] Xiuying Zhang [1]

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G-yW and HX contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Xiuying Zhang; z_xy@jlu.edu.cn

ABSTRACT

Introduction Postoperative malnutrition is a major issue in patients with gastric cancer. The European Society for Clinical Nutrition and Metabolism recommends oral nutritional supplements (ONS) as a first-line nutritional therapy to prevent malnutrition in patients with cancer. However, adherence to ONS is unsatisfactory. The overall aim of this study was to evaluate the adherence of patients with gastric cancer to ONS and to explore the promoting and hindering factors.

Methods and analysis In this study, we will use mixed methods with an explanatory sequential approach for data collection and analysis. In the first phase, a 12-week longitudinal study will be performed to identify changes in trends of oral nutritional supplementation adherence in 135 patients with gastric cancer, the impact of adherence on nutritional indicators and clinical outcomes and ONS adherence-related factors. The primary endpoints include patient adherence to ONS, weight, body mass index and grip strength followed by 30-day readmission rate, complications and adverse reactions. In the second stage, qualitative research will be implemented to provide in-depth insight into the quantitative results. Finally, quantitative and qualitative results will be combined for analysis and discussion to put forward suggestions for improving patients' ONS adherence.

Ethics and dissemination This research protocol has been approved by the Ethics Committee of the School of Nursing, Jilin University, China (No. 2019101601). Results will be disseminated in peer-reviewed journals and conferences, and sent to participating practices.

Trial registration number ChiTR2000032425.

Strengths and limitations of this study

- This protocol first details a complex and deeper understanding of oral nutritional supplement (ONS) adherence in patients after gastric cancer surgery using mixed methods with an explanatory sequential approach.
- Based on the definition of adherence, we will use two indicators, namely, dose and time, to measure patient adherence and will divide patient adherence into four situations to evaluate the effect of four adherence situations on nutritional outcome indicators.
- The qualitative phase will be performed to gain an in-depth understanding of the factors leading to changes in the adherence of patients with gastric cancer taking ONS over 12 weeks, it is very important for future strategies to improve patient adherence to ONS after gastric cancer surgery.
- Due to the restrictions of China's reimbursement policy, patients cannot be fully reimbursed for the ONS taken for 12 weeks, so when enrolling patients, selection bias may arise due to different economic conditions, thereby affecting patient adherence.
- The doctor will be prescribing ONS for 2 weeks, and all patients will purchase them by themselves until 12 weeks after the operation, which may lead to information bias and potentially leading to higher patient adherence in the first 2 weeks.

INTRODUCTION

As the fifth most common malignancy and the third most common cause of cancer-related deaths in the world, gastric cancer accounted for 841 000 deaths in 2013.[1] Radical gastrectomy remains the primary treatment for gastric cancer.[2] However, patients' gastric reservoir function is depleted after surgery,[3] leading to dramatic weight loss within the first 3 months post gastrectomy.[4] Studies have shown that 19%–83% of patients suffer from malnutrition following gastrointestinal surgery,[5–7] and their malnutrition status can take up to 1 year to recover.[4]

Malnutrition is associated with increased postoperative complications and morbidity,[8 9] reduced quality of life[6] and longer hospital stays.[10] Furthermore, malnutrition 3 months after surgery was significantly associated with reduced overall survival (OS) and cause-specific survival (CSS) in patients with gastric cancer.[4] Therefore, it is of great significance

to prevent malnutrition in patients with gastric cancer after surgery.

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends oral nutritional supplements (ONS) as a type of enteral nutrition to prevent malnutrition in patients with cancer.[11] Studies have shown that ONS improves the nutritional status of patients with cancer after surgery.[12 13] A previous study showed that taking ONS for 12 weeks prevented patients from losing 1.1 kg (2% of body weight) after surgery.[14] However, adherence to ONS is unsatisfactory, with rates as low as 42%.[15] Therefore, improving patient adherence to ONS is crucial to maintaining the nutritional status of patients with gastric cancer.

At present, studies on ONS adherence in postoperative gastric patients are limited. Adherence is often described in previous studies as a secondary outcome indicator, so these studies provided limited reference for the development of ONS strategy for postoperative gastric patients. Although ONS is a first-line nutritional therapy recommended by ESPEN,[11] not all countries routinely prescribe ONS to prevent malnutrition in patients with cancer.[16 17] Some studies have found that patients' illness perceptions affect medication adherence,[18 19] and patients' illness perceptions will change over time.[20] Therefore, the research presented above leads to the assumption that the adherence of ONS will show a dynamic change in postoperative gastric patients. Given that patients may need to take ONS for a long time, it is important to explore the reasons for low patient adherence to gain a deeper understanding of the reasons patients decide to continue or stop taking ONS from their perspective. In this paper, we describe a mixed methods protocol for examining dynamic ONS adherence changes and exploring barriers and facilitators of ONS adherence in patients after gastric cancer surgery, which provides an explanatory sequential approach to bring in-depth insight into ONS adherence in patients after gastric cancer surgery. We present the following article in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting checklist (available in online supplemental appendix 1).

AIMS, OBJECTIVES AND RESEARCH QUESTIONS

Study aims

The overall aim of this study is to evaluate the adherence of patients with gastric cancer to ONS, explore the promoting and hindering factors, and provide a reference for the formulation of relevant strategies for ONS adherence in patients after gastric cancer surgery in the future.

The main research questions

- How will adherence change in patients taking ONS for 12 weeks after gastric cancer surgery?
- How will different situations of adherence affect nutritional indicators and clinical outcomes?
- What factors cause differences in the adherence of patients to ONS after gastric cancer surgery?
- How do patient experiences differ with respect to different adherence rates to ONS after gastric cancer surgery?

The objectives of the study

The first phase: objectives of the quantitative study

- Determine the levels and changes in gastric cancer patient adherence to ONS at different follow-up points.
- Determine the relationship between patient adherence and nutritional indicators, such as weight, body mass index (BMI), grip strength, 30-day readmissions, complications and adverse reactions.
- Determine the association between adherence to ONS and demographic characteristics of patients (age, sex, living arrangement and so on) and the texture of ONS.

The second phase: objectives of the qualitative study

- Further explore factors that promote and hinder gastric cancer patient adherence to ONS in the quantitative study.
- Explore factors not found in the quantitative study that may affect patient ONS adherence.

METHOD AND ANALYSIS

Study design

This study will use an explanatory sequential mixed method design to identify the change in trends of ONS adherence and explore barriers and facilitators to adherence in patients after gastric cancer surgery. The study design includes two phases[21] (figure 1). In the first phase, we will conduct a 12-week longitudinal study to observe changes in the adherence of patients on ONS after gastric cancer surgery and to identify factors affecting differences in adherence. After statistical analysis of the quantitative data, we will design and perform the second qualitative phase of the study. 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. Finally, quantitative and qualitative results will be combined for discussion. Quantitative research will begin in March 2021 and is expected to be completed in July 2021. The qualitative research will follow in August 2021.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of this research.

Stage 1: quantitative study

We will conduct a 12-week longitudinal study (each week will serve as a follow-up point) to evaluate adherence to ONS in patients with gastric cancer after surgery. At the same time, we will also evaluate the relationship

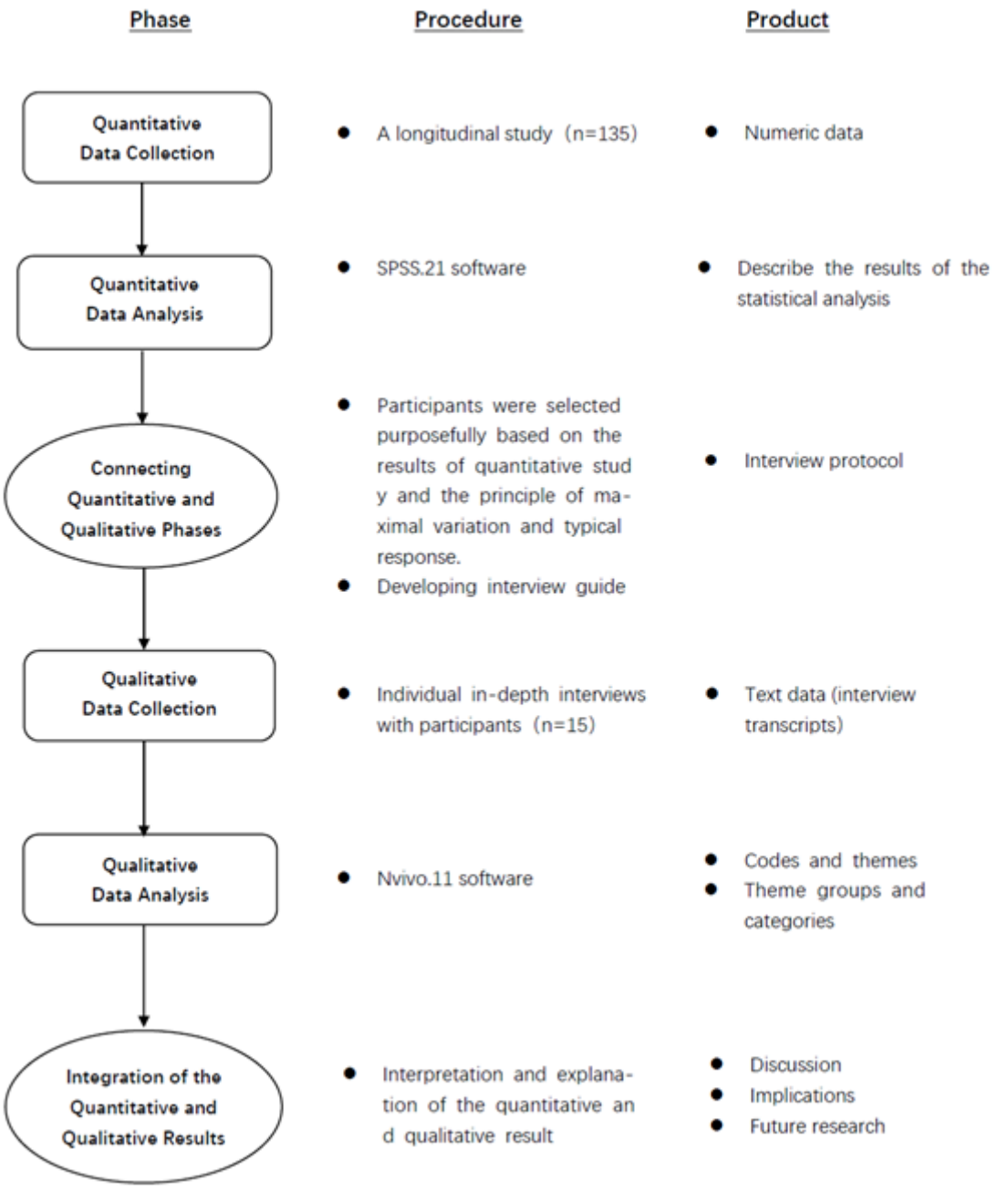

Figure 1 Study diagram.

between adherence and body weight, BMI, grip strength, 30-day readmissions, complications and adverse reactions (figure 2).

Sample size and sampling method

Sample size was calculated based on the Bunout *et al* study.[22] Considering α=0.05 and $Z_{\alpha/2}$=1.96, the sample size needed was estimated to be 113. Assuming a 10% dropout rate and 10% mortality, the final sample size was determined to be 135. The calculation formula is as follows: $n= (Z\alpha/2\sigma/\delta)^2$.

Before this study, we found that not all doctors routinely prescribed ONS to prevent malnutrition in patients with cancer in China. A physician order for ONS is a prerequisite for patient adherence to ONS, so we will use the purposive sampling method to select patients who already have an ONS prescription during the first 7 postoperative days in the gastrointestinal surgery department of a tertiary class hospital in Jilin Province. A member of the research team will explain the study to patients, and eligible patients will be invited to join the study and sign the informed consent form. Inclusion and exclusion criteria are shown in table 1.

Data collection and schedule

Baseline data collection

Collection of quantitative data will begin after obtaining informed consent. Demographic and socioeconomic data and clinical backgrounds will be collected through a general information questionnaire. Body weight (in kg),

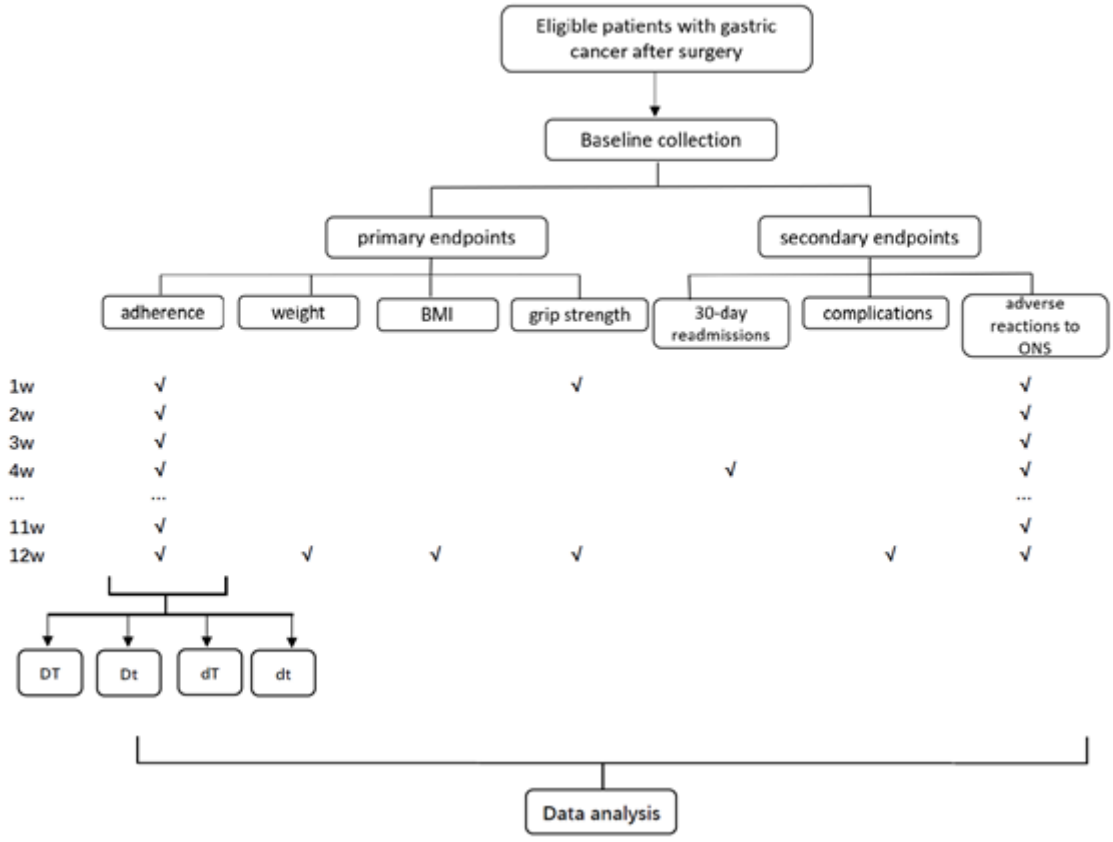

Figure 2 Quantitative study design flow chart. BMI, body mass index; dt, both the dosage and the number of days did not meet the doctor's requirements; DT, both the dosage and the number of days meet the doctor's requirements; dT, the daily dosage did not meet the doctor's order, and the days of taking reached the prescribed days; Dt, the daily dosage reached the prescribed amount, and the days of taking did not meet the doctor's requirements; ONS, oral nutritional supplements; W, week.

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
► Patients with stage I, II or III gastric cancer were diagnosed by pathology before surgery	► Diagnosis of double cancer
► Patients who had distal or total gastrectomy	► Allergy to milk, soy bean, wheat or salmon
► Age 18 years or order	► Patients with mental illness, impaired consciousness and inability to communicate normally
► PG-SGA Grades B or C	
► No gastrectomy, radiation, chemotherapy before surgery	
► Patients have the ability to ingest food orally	
► Patients or his/her family members had a smartphone on which they could use WeChat*	
► Patients written informed consent	

*WeChat: as one of the popular social media apps in China.

BMI and grip strength will be assessed preoperatively to monitor patients' nutritional status.

Primary endpoints

The primary endpoints include patient adherence and nutritional status at 12 weeks post gastrectomy (weight, BMI, grip strength). Details of the schedule are described in table 2.

Adherence will be measured through the patient's 'weekly ONS diary'. In this study, ONS will be prescribed by the patients' attending physician, who will prescribe 400 kcal of ONS to the patient every day. Patients' attending physician will prescribe liquids or powders according to her/his usual practice. When ONS is prescribed, a researcher will record ONS-related factors, including name and texture. After discharge, participants will be required to keep a daily 'weekly ONS diary', including the amount of daily ONS consumed and adverse reactions. Each patient in the study will be enrolled in a group chat on WeChat (as one of the popular social media apps in China, WeChat is widely used for patient disease guidance and education[23]), and the researcher will ask patients for 'weekly ONS diary' photos by WeChat at each follow-up time point. Patient weight, BMI and grip strength will be remeasured 3 months after surgery when the patient is re-examined.

Table 2 Content for the schedule of enrolment and assessments

Study period													
	Enrolment	Post-allocation (12 weeks)											Close-out
Time point	Day −7~0	1	2	3	4	5	6	7	8	9	10	11	3 months
Enrolment													
Eligibility screen	×												
Informed consent	×												
Baseline data	×												
ONS-related factors	×												
Assessments													
Primary endpoints													
Adherence		×	×	×	×	×	×	×	×	×	×	×	×
Body weight	×												×
BMI	×												×
Grip strength	×												×
Secondary endpoints													
30-day readmissions					×								
Complications													×
Adverse reactions		×	×	×	×	×	×	×	×	×	×	×	

BMI, body mass index; ONS, oral nutritional supplements.

To rule out the effects of daily oral food intake on the study results, calories in the patient's daily diet will be calculated at each follow-up based on the local dietary assessment form (1–5 points) in China.[24]

Secondary endpoints

Secondary endpoints are as follows: (1) 30-day readmissions, where readmission will be defined as return to hospitalisation for any disease diagnosed within 30 days after surgery; (2) infective complications, which will include wound infection, respiratory tract infection and infective diarrhoea[12 25]; and (3) adverse reactions to ONS, which will include bloating, diarrhoea, nausea and vomiting.[26] Details of the schedule are described in table 2.

To illustrate overall trends of ONS adherence in patients with gastric cancer after surgery over time, we will calculate the adherence by proportion of ONS consumed (the percentage of prescribed dosage consumed)[17] and create the ONS adherence curve based on the average ONS adherence at each time point. Adherence is defined as 'Voluntary cooperation of the patient in taking drugs or medicine as prescribed. This includes timing, dosage, and frequency.'[27] Adherence does not only encompass dose adherence but also includes duration of use, so we will use the second method to calculate adherence by the proportion of days covered (the percentage of prescribed days covered).[28] To elucidate the status of ONS adherence in patients at different time points and provide heterogeneous samples representing different levels of adherence for subsequent qualitative studies, we will use both methods to describe adherence changes. The following four situations will occur at this point: (1) both the dose and the number of days meet the doctor's requirements (DT); (2) the daily dose reached the prescribed amount, but the days of taking ONS did not meet the doctor's requirements (Dt); (3) the daily dosage did not meet the doctor's order, but the days of taking ONS reached the prescribed days (dT); and (4) neither the dosage nor the number of days met the doctor's requirements (dt). Therefore, at each time point, patients will be divided into four groups according to their adherence. Next, we will use a bar graph to illustrate the proportion and changes among the four groups of people at different time points. Finally, we will compare differences in outcome indicators among the four groups (figure 2).

Measurement data will be described as the mean (SD), independent sample t-tests will be used to compare the average level of independent data, and paired sample t-tests will be used to compare the average level of paired data. One-way analysis of variance will be used to compare data in different groups, and pairwise comparisons will be performed with the Least-Significant Difference method. Categorical variables will be expressed as percentages, and the χ^2 test will be used for comparisons between groups.

Stage 2: qualitative study

In this stage, we will conduct qualitative research to explain the results of the quantitative phase and further explore barriers and facilitators of adherence to ONS from the perspective of patients with gastric cancer (figure 3).

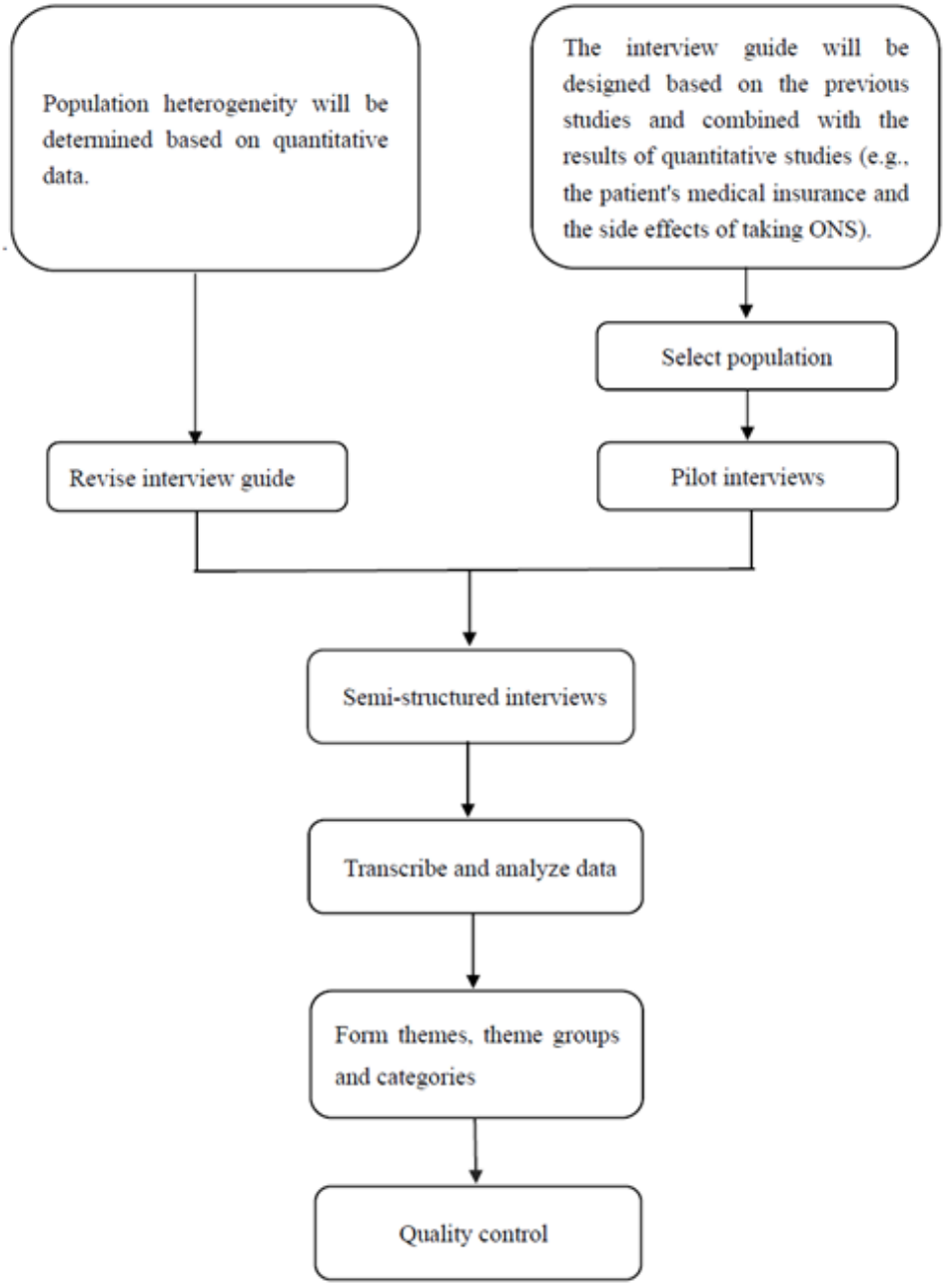

Figure 3 Qualitative study design flow chart. ONS, oral nutritional supplements.

Sampling method

We will use purposive sampling to select participants. To ensure the sampling follows the principles of typical response and maximal variation, we will select participants who represent the results of the quantitative phase (they differ in age, education, income, adherence and other aspects) to better explain the quantitative research with qualitative research. Recruitment of patients will be discontinued when the qualitative data become saturated.[29]

Designing the interview guide

In this explanatory sequential mixed methods study, designing the interview guide will be an important link between the qualitative and quantitative research. The quantitative results will not only guide the sampling procedure but also point towards questions in the qualitative phase. We will design interview guides for qualitative research based on the results of quantitative research. The qualitative data will provide more depth and insight into the quantitative results. In addition, we will give the formed interview guide to a psychologist for review so that the interview can proceed more smoothly and obtain more effective information. Pilot interviews will be conducted with a small number of participants, and the interview guide will be further revised according to the information obtained from the pilot interviews. By doing

this, we will ensure that the interview guide will be culturally sensitive and easier for patients to understand.

Data collection

Data will be collected using open-ended questions through in-depth semistructured interviews. The interview will begin with the question 'How well are you recovering?' To understand patient perceptions of ONS, we will ask, 'Do you feel that ONS has any effect on your recovery from the disease?' Then, based on the results of the first phase of the study, we will ask patients who have different types of adherence questions, such as 'Can you tell me why you stopped taking ONS?' 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 interview, we will use 'Why?', 'What do you mean?', and 'Can you explain this?' to further understand patients' experiences. To ensure that effective information is obtained from the interview, all patients will be interviewed in a comfortable setting. Following consent, interviews will be recorded and transcribed verbatim. During the interview, we will record non-verbal data from patients in a notebook, such as intonation, movements, gestures, expressions and so on.

Data analysis

In our study, data collection and analysis will be conducted simultaneously. After each interview, researchers will transcribe the recording into words in a timely manner and mark the emotional responses of interviewees in the corresponding position of the text. To preserve the original style of the data, we will use the patient's dialect whenever possible. We will use NVivo and Colaizzi's seven-step analysis methods to manage and analyse qualitative data, respectively. Researchers will carefully and repeatedly read all interview materials and extract relevant statements and meanings. Then, researchers will search for common concepts or characteristics of meanings and form themes, theme groups and categories.

Validity and reliability/rigor

'Rich rigour,' 'sincerity,' 'credibility' and 'resonance' are elements suggested by Tracy as denoting excellence in qualitative research.[30] To improve and verify the accuracy of the results, we will give the transcript of the interview to the interviewees so that the patient can confirm whether the content is comprehensive. If there is any other content they want to add, they can add to the data directly. The corresponding author will read the content of the interview repeatedly to determine whether the results resonate with similar people, and the extracted text that contains themes will be reviewed by all the authors and thoroughly discussed. To ensure the codes and topics are professional and accurate, we will submit the generated codes and topics to psychologists for review. In addition, we will provide examples of the initial codes to other researchers who are not involved in this study to determine whether they have similar perceptions based on the text.

DISCUSSION

A previous study reported that the 12-month mortality rate is 26% among malnourished patients with gastric cancer.[4] ONS is the preferred method of nutritional therapy, and some studies have shown that the effect of ONS is dose-dependent,[31–33] so maintaining high adherence to ONS plays an important role in the postoperative recovery of patients with gastric cancer. At present, adherence to ONS is generally low. Therefore, we need to identify the relevant factors affecting adherence to ONS in patients with gastric cancer. This is the first study to explore adherence to ONS in patients after gastric cancer surgery and will be performed via a mixed methods approach.

Malnutrition often leads to muscle dysfunction, especially thoracic muscle dysfunction, which often leads to pneumonia.[34] Patients with malnutrition often develop impaired intestinal immune function that further aggravates nutrient digestion and absorption dysfunction.[35 36] In addition, patient wound healing is also markedly affected by the state of malnutrition.[37] Therefore, in our study, in addition to using body weight, BMI and grip strength as indicators to assess patients' nutritional status, we will also use complications, including wound infection, respiratory tract infection, and infective diarrhoea, and 30-day readmission rate as indicators to assess patients' postoperative recovery.

In other similar clinical studies, patient self-reporting was used to measure adherence, similar to using a patient's 'daily food diary' to record their daily intake (diet+ONS).[38] We think that in our study, since the elderly (≥65 years) make up a large portion of the participants, it would be difficult for patients to keep track of their diet in detail.[17] Therefore, we will use an 'ONS diary' instead of a 'daily food diary' to record the dose of ONS consumed, and at each follow-up time, we will estimate patients' energy intake according to the 'Chinese diet assessment tool'. According to the assessment, the range corresponding to the score of this tool is 90%, in accordance with the results of the standard diet survey.[24] In addition, this scale has been used in other studies as a nutritional assessment tool.[39 40]

Due to China's medical policy, each doctor can only prescribe an approximately 2 week dose of ONS to patients, and patients will buy ONS at the community pharmacy when all their prescribed ONS has been used up. At present, in the Chinese market, the texture of ONS is primarily powder and liquid, but to observe the impact of different texture types of ONS (liquid or powder) on patient adherence, we will keep the original style of doctors prescribing ONS in our study. However, regardless of whether powder or liquid, we will use intact protein-based ONS.

To explore factors that facilitate and present barriers to patient adherence to ONS, we will use a mixed methods

approach. This approach not only has the advantages of quantitative and qualitative research but also overcomes the limitations of the separate study approach. Recently, there was a quantitative study on ONS adherence in patients after gastrointestinal cancer surgery,[26] but it only identified barriers to adherence of ONS based on reviewing previous studies to extract frequent reasons, without an in-depth understanding of patients' feelings, which may have limited the results. In other studies, changes in patient adherence to ONS at different times after surgery were not compared, which may lead to new findings in our study. Therefore, this study will have a more comprehensive and in-depth understanding of the facilitators and barriers of patient ONS adherence. To our knowledge, this method has not been previously used to specifically understand the influencing factors of ONS adherence in this group of patients. The key output of this study will be practice recommendations in relation to the development of an ONS strategy for postoperative gastric patients.

ETHICS AND DISSEMINATION

This research protocol has been approved by the Ethics Committee of the School of Nursing, Jilin University, China (No. 2019101601). Results will be disseminated in peer-reviewed journals and conferences, and sent to participating practices.

Author affiliations
[1]Department of Fundamental Nursing, School of Nursing, Jilin University, Changchun, China
[2]Department of Histology & Embryology, College of Basic Medical Sciences, Jilin University, Changchun, China
[3]Department of Surgical Nursing, School of Nursing, Jilin University, Changchun, China
[4]Institution of Sports Medicine of Third Hospital, Peking University Third Hospital, Beijing, China

Contributors Conception and design: G-YW, HX, X-YZ. Administrative support: HX. Provision of study materials or patients: HX, HY, XW. Collection and assembly of data: G-YW, HX, H-QL, X-YZ. Data analysis and interpretation: G-YW, HX. Manuscript writing: All authors. Final approval of manuscript: All authors.

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ORCID iD
Xiuying Zhang http://orcid.org/0000-0001-6006-2914

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39 Shi HP, Chen W, Yang LQ. Fighting malnutrition in hospital: an introduction to hunger-free Hospital programme. *Electron J Metab Nutr Cancer* 2018;5:6.
40 Tian BW, Zhang JT, Zhang GY. Observation on the effect of grading and filing of nutrition intervention in patients with digestive tract cancer. *Journal of Nursing* 2019;26:4.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1/1-3	title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2/24-25	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	not applicable	not applicable
Protocol version	3	Date and version identifier	2/24-25	Abstract
Funding	4	Sources and types of financial, material, and other support	2/28-32	title page
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1/6-20	title page
	5b	Name and contact information for the trial sponsor	1/22-24	title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1/15-20	title page
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	not applicable	not applicable
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2/8-4/3	manuscript
	6b	Explanation for choice of comparators	4/4-21	manuscript
Objectives	7	Specific objectives or hypotheses		

			4/22-5/8	manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)		
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4/87-5/95	Study design
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-115	Sample size and sampling method
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	not applicable	not applicable
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	not applicable	not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	not applicable	not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable	not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6/122-7/146	Data collection and schedule
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7/146-147	Data collection and schedule
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5/104-107	Sample size and sampling method
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5/108-6/115	Sample size and sampling
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	not applicable	not applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	not applicable	not applicable

			not applicable	not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	not applicable	not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	not applicable	not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6/117-7/147	Data collection and schedule
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6/117-7/147	Data collection and schedule
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7/149-8/176	Data analysis
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7/149-8/176	Data analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7/149-8/176 7/149-8/176	Data analysis Data analysis
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14/305-307	Footnote
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14/308-15/317	Footnote
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	not applicable	not applicable
			11/225-235	Validity and reliability/rigour

Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14/308-15/317	Footnote
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	not applicable	not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	2/24-25	Abstract
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15/314-317	Footnote
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14/305-307	Footnote
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	not applicable	not applicable
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	not applicable	not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	not applicable	not applicable
	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	not applicable	not applicable
Appendices			not applicable	not applicable
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates		
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Available on request to authors	Available on request to authors
			not applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.