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GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

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ABSTRACT (295 words)

Introduction

Elderly cancer patients often have age-related physical and psychosocial problems that should be fully shared with their oncologists. Geriatric Assessment (GA) can assess these age-related problems and guide management. Communication support might also facilitate implementation of GA-guided management. We will conduct a multicenter, randomized controlled trial to examine the efficacy of a program that combines a GA summary, management recommendations, and communication support to facilitate age-related communications between elderly Japanese cancer patients and their oncologists, and thus to implement program-guided management.

Methods and analysis

We plan to recruit a total of 210 patients aged 70 years or older, diagnosed with incurable cancers of gastrointestinal origin, and referred for first- or second-line chemotherapy. In the intervention arm, a summary of management recommendations based on a GA and Question Prompt List (QPL) will be provided to patients and shared with their oncologists at the first outpatient visit after randomization by trained intervention providers. For five months after the initial intervention, implementation of

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GA-guided management recommendations will be reviewed monthly with the patients and their oncologists to implement management as needed. The GA and QPL will be re-evaluated at three months, with a summary provided to patients and their oncologists. Those participants allocated to the usual care arm will receive usual oncology care. The primary endpoint is the number of conversations about age-related concerns at the first outpatient visit after randomization.

Ethics and dissemination

This study was approved by the Institutional Review Board of the National Cancer Center Japan on April 15, 2021 (ID: 2020-592). Study findings will be disseminated through peer-reviewed journals and conference presentations.

Trial status

The study is currently recruiting participants and the enrollment period will end on March 31, 2024, with an expected follow-up date of March 31, 2026.

Trial registration number UMIN000045428.

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Key words: Communication, decision making, Geriatric Assessment, patient-centered care, patient-physician relationship, quality of life, Question Prompt List

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ARTICLE SUMMARY

Trial registration: The protocol was registered on September 13, 2021 at the UMIN Clinical Trials Registry (Registration No. UMIN000045428).

Data statement: The study protocol, data definition tables, and dataset will be uploaded to the UMIN-Individual Case Data Repository at https://www.umin.ac.jp/icdr/index-j.html.

Protocol version: The protocol was updated to version 6.0 on January 17, 2022.

Strengths and limitations of this study:

- This is the protocol paper of a multicenter, randomized controlled trial to examine the efficacy of a program that combines a Geriatric Assessment (GA), GA-guided management, and communication support using a Question Prompt List (QPL) for elderly Japanese cancer patients.
- With the aim of facilitating future implementation, this study will use a self-reported GA and QPL administered via a web-based application to generate a GA summary, tailored recommendations, and patients' selected questions.
- Due to the nature of the intervention, both patients and their oncologists would be

aware of the allocated arm, which could potentially influence care during treatment.

- The intervention program is complex, consisting of a multifactorial component (GA summary, management recommendations, and communication support using QPL), making it difficult to determine each component's contribution to the outcomes.
- Because this study is limited to patients with gastrointestinal cancers, its generalizability to other cancers will not be clarified.

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INTRODUCTION

Many cancers are age-related diseases. Japan is a front-runner of the super-aged societies, which is defined as greater than 21% of a population being 65 years or older,[1] and its number of elderly cancer patients is increasing. In Japan, more than 70% of cancer incidences and 80% of cancer mortality occur in patients aged 65 years and older.[2 3] However, elderly patients are often excluded from clinical trials and they face difficulty due to lack of evidence for treatment decisions.[4] Elderly cancer patients are physically, psychologically, and socially heterogeneous; they differ from their younger counterparts in terms of physical function, psychological well-being, life circumstances, and values and preferences.[5] Therefore, the treatment and care of elderly cancer patients is complex and should be individualized. Subjective assessment by oncologists based on performance status and chronological age is inadequate to cope with these heterogeneous conditions, which can lead to overtreatment or undertreatment. The concept of geriatrics, which evaluates elderly patients in a multifaceted and comprehensive manner, is necessary in oncology.

Comprehensive Geriatric Assessment (CGA) is a multidimensional, interdisciplinary diagnostic process that focuses on determining the medical, psychosocial, and functional capabilities of elderly adults in order to develop a

coordinated and integrated plan for treatment and long-term follow-up.[6] In geriatrics, CGA has been shown to reduce mortality, decrease institutionalization and readmission, and improve cognitive and physical functioning, mainly through interventions by a multidisciplinary team.[7 8] The term "geriatric assessment" (GA) is commonly used in oncology instead of CGA because CGA research in oncology has studied mainly the diagnostic process for selecting appropriate treatment through assessment of age-related problems without a thorough focus on geriatric interventions for these problems.[9] Recently published randomized controlled trials in the United States have demonstrated that feedback in the form of a GA summary and GA-guided management recommendations to patients and their oncologists facilitates communication about age-related concerns, thereby reducing incidences of serious adverse events related to chemotherapy.[10 11]

Patient-centered communication is important to help patients prioritize their concerns, ensuring that decisions are in line with their values and preferences. Although studies have shown benefits of communication interventions to facilitate patient-centered communication,[12 13] these interventions were not tailored to address age-related concerns of elderly cancer patients. In fact, many elderly cancer patients have age-related symptoms that are not identified, communicated, or addressed in daily oncology

practice.[14] Communication interventions might help elderly cancer patients and their oncologists share and manage age-related problems by recognizing these conditions that are often overlooked in daily oncology practice.

Elderly cancer patients in Japan are less likely to communicate their values and preferences regarding treatment to their physicians; therefore, they need support to express their intentions and preferences based on their values.[15] A Question Prompt List (QPL) is a list of specific questions that helps patients express their intentions by facilitating communication with their healthcare providers and encouraging them to ask their healthcare providers questions.[16] A systematic review has shown that use of a QPL increases the number of questions that patients ask their physicians.[17] We previously conducted a randomized controlled trial on the usefulness of QPL in Japanese patients with advanced cancer undergoing initial anticancer therapy and found that patients perceived the materials, including the QPL, to be useful for understanding their treatment plans.[18]

We hypothesize that feedback in the form of only a GA summary and GA-guided management recommendations to patients and their oncologists would be insufficient for elderly cancer patients in Japan to express their age-related concerns. Therefore, this study will examine the efficacy of a program that combines a GA summary, GA-guided

management recommendations as provided by a multidisciplinary team, and communication support using QPL, with the aim of facilitating communications between elderly cancer patients and their oncologists and implementing GA-guided management.

METHODS and ANALYSIS

This protocol was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and SPIRIT PRO Extension Guidelines.[19 20]

Study design

This study is a single-blind (outcome assessor blind), parallel-group randomized controlled trial conducted at the National Cancer Center Hospital and Kyorin University Hospital. The study period of this trial is from April 2021 to March 2026; the registration period is from September 2021 to March 2024.

This study protocol was reviewed and approved by the protocol review committee of Japan Supportive, Palliative, and Psychosocial Oncology Group as a J-SUPPORT 2101 study and the institutional review boards at each participating institution.

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Inclusion and exclusion criteria

Enrolled patients must satisfy the following inclusion criteria: (1) diagnosis of esophageal, gastric, colorectal, hepatic, biliary tract, or pancreatic cancer; (2) incurable disease (locally advanced stage III, IV, or recurrent); (3) age 70 years or older; (4) ECOG Performance Status score of 0–2; (5) scheduled to receive first- or second-line chemotherapy; (6) able to read, write, and understand Japanese; (7) provide written informed consent for trial participation; and (8) have at least one impairment of GA domains other than polypharmacy at the time of registration.

Participants will be excluded if they meet any of the following exclusion criteria: (1) scheduled to undergo surgery within three months; (2) participating or planning to participate in other interventional studies for which intervention by this study would be undesirable (e.g., other psychological or communication support studies, clinical trials, etc.); or (3) judged to have difficulty participating in the study by attending oncologists.

Screening

Trained study staff will review a list of potentially eligible patients and approach patients consecutively with permission from their oncologists. All elderly cancer patients who meet inclusion criteria (1) through (7) will be registered and screened for GA.

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Patients having any GA impairment other than polypharmacy will be randomly assigned to either the intervention arm or the usual care arm (Figure 1).

Geriatric Assessment

All participants will undergo a GA that evaluates eight domains (falls, functional status, psychological status, nutrition, social support, cognition, polypharmacy, and comorbidity) using electronic patient-reported measures at baseline. Assessment items include (1) history of falls in the past six months; (2) Instrumental Activities of Daily Living (IADL) subscale of the Multidimensional Functional Assessment Questionnaire, Older American Resources and Services (OARS);[21] (3) Patient Health Questionnaire-9;[22] (4) Mini-Nutritional Assessment;[23 24] (5) living alone and/or with limited support; (6) Mini-Cog;[25] (7) number of medications; and (8) Charlson Comorbidity Index[26] (Table 1).

Table 1. Geriatric Assessment (GA) Tools

GA Domain	Assessment Tools	Cut-off Points
Falls	History of falls in the past 6 months	Any history of falls
Functional Status	The Instrumental Activities of Daily Living (IADL) subscale of the Multidimensional Functional Assessment Questionnaire; Older American Resources and Services (OARS)[21]	Any IADL deficit
Psychological Status	Patient Health Questionnaire-9[22]	≥5 points

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Nutrition	Mini Nutritional Assessment[23]	≤11 points
Social Support	Living status, assistance	Living alone and/or without any assistance
Cognition	Mini-Cog[25]	≤2 points
Polypharmacy	Number of medications	≥5 regularly scheduled prescriptions
Comorbidity	Charlson Comorbidity Index[26]	≥3 points

These selected assessment tools are based on the American Society of Clinical Oncology guidelines, Japan Clinical Oncology Group geriatric research policy, and previous clinical trials.[10 11 14 27-29] Once these GA measures are entered via a web-based application that was developed in a previous study[30] and customized for the present study, a GA summary and management recommendations tailored to each patient will be generated as a PDF file. This summary will contain information on GA impairments and GA-guided management recommendations based on literature reviews, guidelines, previous clinical trials, and expert consensus[10 11 14 27-29 31] (Table 2). All assessments, other than cognitive and comorbidity measures performed by the study staff, will be self-administered on a touchscreen tablet. The study staff will assist patients who cannot independently complete the assessment.

Table 2. Geriatric Assessment-Guided Management Recommendations

GA Impairments	Recommendations

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Any history of falls Any Instrumental Activities of Daily Living (IADL) deficit	1. Referral to physical therapy and/or occupational therapy 1-1. Strength and balance training; introduce home exercise program 1-2. Assist according to IADL disability 1-3. Provide support according to falling risk 2. Referral to medical social workers and/or nurses 2-1. Provide support according to IADL disability 2-2. Evaluate home safety, adjust environmental factors (fall prevention), and use nursing care services 3. Review falling risk due to polypharmacy and adjust medications as needed (referral to pharmacist)
Patient Health Questionnaire-9 ≧5	1. Referral to a psychologist and/or psychiatrist 1-1. Cognitive-behavioral therapy and pharmacotherapy 2. Referral to medical social workers and/or nurses 2-1. Referral to hospital-based psychological support services 2-2. Referral to local social activities (e.g., community comprehensive support center)
Mini Nutritional Assessment ≦11	1. Referral to a dietician 1-1. Assess nutritional status; provide nutritional guidance 1-2. Provide information materials and brochures 1-3. Provide information on nutritional supplements; prescribe nutritional supplements 2. Referral to social workers as needed (assistance with shopping and meal preparation)
Living alone and/or without any assistance	1. Referral to medical social workers and/or nurses 1-1. Apply for long-term care insurance; referral to community comprehensive support center 1-2, Referral to transportation services, home care/nursing care, and support group 1-3. Identify and establish key persons in case of anyone's absence
Mini-Cog ≦2	1. Referral to a cognitive specialist or memory clinic (psychiatrist or neurologist) 1-1. Evaluate decision-making ability and capacity to consent as needed 1-2. Counsel on risk of delirium; reduce medications at risk of delirium 2. Encourage family/caregivers to participate in consultation and treatment decisions 3. Reduce the number of medications or adjust dosage and administration

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	(referral to a pharmacist)
≧ 5 medications Charlson Comorbidity Index ≧3	1. Referral to a pharmacist 1-1. Reduce the number of medications or adjust dosage and/or administration 1-2. Discontinue potentially inappropriate medications (PIMs) 2. Consult with nurses and/or a pharmacist to confirm adherence 2-1. Determine patient's understanding of medication, missed doses, and patient's ability to manage medications and decipher text on a medication bag 3. Involve family and caregiver in treatment decisions and management of comorbidities 4. Review prescriptions and management of comorbidities by family physicians, geriatricians, and other specialists

Note. GA = Geriatric Assessment.

Randomization

Participants will be randomly allocated (1:1) to an intervention arm or a usual care arm (Figure 1). Computer-generated random allocation sequences will be provided and centrally controlled by an independent data center. A stratified block-randomization method will be used to ensure balanced allocation by study site, cancer type (esophageal, gastric, colorectal, hepatic, biliary tract, or pancreatic), and line of treatment (first or second). Allocation results will be sent electronically to the study staff at each institution. Participants and their oncologists will remain unblinded due to the nature of the interventions.

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Intervention

GA summary and management recommendations

In the intervention arm, a GA summary and management recommendations will be presented to the patients and their oncologists at the first outpatient visit after randomization. An intervention provider will explain the GA summary to the patient and then discuss the patient's perceptions, need for recommended management, resources available at each institution, and other specific issues. An intervention provider will prepare a feedback sheet based on information obtained from the patients, such as age-related concerns and their interest in the recommendations, to reduce oncologists' burden. Oncologists will have autonomy to incorporate into their practice whatever recommendations are deemed necessary. The multi-disciplinary team at each institution will implement management recommendations with referrals from an oncologist based on clinical judgement. An intervention provider may help implement management recommendations with an oncologist's approval.

For five months after the initial intervention, implementation of GA-guided management recommendations will be reviewed monthly with the patients and their oncologists to implement management as needed. Three months after the initial intervention, the GA will undergo reevaluation, and a GA summary, management

recommendations, and a feedback sheet will be provided to the patients and their oncologists so that GA-guided recommendations can be modified and implemented as needed.

Oncologists will receive a 20-min lecture on how to most effectively utilize GA information in their clinical practice for elderly cancer patients. The lecture will include an overview of the usefulness of GA and GA-guided management in oncology.

Communication support using QPL

In this study, a QPL that was developed based on our previous studies[18 32 33] to support shared decision-making for treatment of elderly cancer patients will be used to facilitate communications with attending oncologists. The QPL consists of 75 questions categorized into eight topics (i.e., diagnosis and disease stage, current and future treatments, management of current and possible future symptoms, daily life activities, care and expected prognosis after standard treatment, needs of caregivers, psychological distress and management, and values) and a free-writing section for other age-related questions based on the opinions of elderly cancer patients, oncologists, and geriatricians.

Patient communication coaching using the QPL consists of three parts: (1) reading a list and selecting questions that the patient prefers to discuss with their

oncologists, and prioritizing selected questions via a web-based application; (2) discussing the reasons for and background behind selecting the questions, and identifying difficult questions to ask; and (3) practice asking their oncologists these questions. Patients are given a 14-page A4 size QPL brochure for reference after the intervention. An intervention provider will prepare a feedback sheet, including a list of selected questions rephrased in the patients' own words, if necessary, for patients to present to their oncologists before the first outpatient visit after randomization.

Three months after the initial intervention, an intervention provider will provide communication support using QPL and a feedback sheet for patients to present to their oncologists along with their GA results.

All interventions will be provided by intervention providers who are clinical psychologists, nurses, physicians, or hospital staff who have participated in intensive training using an intervention manual. Intervention providers will hold weekly meetings to review all intervention sessions with supervision by the primary investigator to maintain quality.

In the usual care arm, participants will receive usual oncology care. Participants and their oncologists will not receive GA results at the time of registration unless severe cognitive or psychological problems are revealed.

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Concomitant treatments will not be restricted.

Stopping rules for participants

The protocol intervention will be discontinued under the following conditions: (1) the attending oncologists deem it necessary to discontinue the intervention; (2) the patient requests discontinuation of the intervention; (3) the patient dies during the intervention period; (4) the patient's condition suddenly deteriorates after registration; (5) a protocol violation or ineligibility is discovered; or (6) the patient withdraws consent to participate in the study. The investigator will report the reasons for the discontinuation of the intervention to the data center. Follow-up assessments, including questionnaires, will continue unless consent is withdrawn.

Assessment measures

Table 3 shows the schedule of outcome measurements.

Table 3. Schedule of Outcome Measurements

	Baseline	Primary registration	Secondary registration	First outpatient visit after GA	Three months	Six months	Twelve months
GA	○				●		
Patient Characteristics*		○					
Number of age-				◎			

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related conversations							
Quality of age-related conversations				◎			
RIAS[39] and SHARE[38]				◎			
CARE-10[40 41]				◎	◎	◎	
TiOS[42 43]				◎			
CTCAE					◎		
Prevalence of dose modifications					◎		
Implementation of GA-guided management					◎	◎	
GA Evaluation		○					
QPL Evaluation				●			
GA+QPL Evaluation				△		△	
PRO-CTCAE[35]			◎		◎	◎	
IADL[21]			◎		◎	◎	
QOL[34]			◎		◎	◎	
Overall survival rate						◎	◎

○ will be evaluated among all participants at the primary registration.

◎ will be evaluated among all participants after the secondary registration.

● will be evaluated among participants in the intervention arm.

△ will be evaluated among attending oncologists in the intervention arm.

*Patient Characteristics include age, gender, highest level of education, employment status, marital status, financial concerns, and self-rated health.

Note. CARE-10 = Consultation and Relational Empathy measure-10,; CARG = Cancer and Age Research Group; CTCAE = Common Terminology Criteria for Adverse Events; IADL = Instrumental

Activities of Daily Living; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QOL = Quality of Life; QPL = Question Prompt List; RIAS = Roter intention analysis system; SHARE = setting, how to deliver bad news, additional information, reassurance, and emotional support; TiOS = Trust in Oncologists Scale; and GA = Geriatric Assessment.

Primary outcome measure

The primary outcome is the number of conversations about age-related concerns during consultation, which is used to evaluate whether the intervention facilitates discussions between patients and their oncologists. At the first outpatient visit within four weeks from the baseline GA, the conversation between patients and their oncologist will be audio-recorded and transcribed verbatim. According to a previous study by Mohile et al[10], a content analysis framework will be used to assess how to identify age-related concerns and whether stated concerns are acknowledged and considered further by the oncologist (quality of discussion) and to determine whether acknowledged concerns motivate implementation of management recommendations. For each transcript, coding will be performed directly by two coders who have received extensive training and supervision by the principal investigator, are blind to the study hypotheses and the allocation, and are not involved in any other aspect of the study.

Secondary outcome measures

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1. Overall survival rate at six and twelve months. Overall survival is defined as the time from randomization to death from any cause or last contact, whichever is earlier.

2. Treatment failure-free survival, which is defined as the time from randomization to treatment discontinuation for any cause or last contact, whichever is earlier.

3. Grade 3–5 chemotherapy-related treatment toxicity is evaluated according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events ver. 5.0 by physicians and/or nurses.

4. Prevalence of dose modification within three months (treatment modification, dose reduction, and/or discontinuation).

5. Unscheduled hospitalization and emergency department visits.

6. Functional status using the OARS-IADL questionnaire[21] (electronic-patient reported outcomes [ePRO]).

7. Quality of life measured by the EORTC Quality of Life-Core 30-item version (QLQ-C30 Questionnaire)[34] (ePRO).

8. Core items (12 symptoms) of the NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system, Japanese version[35-37] (ePRO).

9. The number of geriatric problems successfully addressed for participants in the

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intervention arm.

10. Patient-centered communication behaviors will be analyzed based on impression ratings by two blinded coders. The analysis will utilize audio-recorded oncology visits for all participants and assesses the total score of the 27 SHARE categories: setting, how to deliver the bad news, additional information, and reassurance and emotional support.[38] In addition, patient-preferred communication behaviors will be analyzed using the 40 categories of the Roter intention analysis system (RIAS).[39]

11. Communication satisfaction using the Consultation and Relational Empathy (CARE) measure[40 41] (CARE-10) (ePRO).

12. Trust in Oncologists Scale (TiOS)[42 43] (ePRO).

13. Patients' assessment surveys on the burden and usefulness of the intervention will include "Was it difficult to answer the (GA) questions?" "Did you feel burdened by the (GA) questions?" "Did you feel burdened by the intervention (GA + QPL)?" "Did you find the intervention (GA + QPL) helpful in organizing your thoughts?" and "Did the intervention (GA + QPL) help you talk with your doctor?"

14. Oncologists' assessment surveys on the burden and usefulness of the intervention will include "Was the intervention (GA + QPL) useful to you?" and "Did you feel burdened by the intervention (GA + QPL)?"

Harms

No specific serious adverse events are anticipated for participants in this study. Patients will be subjected to time burdens of 30–40 min for the study intervention and 10–20 min for the GA as well as baseline and follow-up questionnaires. There is no direct financial cost associated with study participation, but we recognize that patients are donating their time to participate. Patients will not be compensated for their participation.

Compensation

If patients develop any unforeseen health issues due to study participation, they will be adequately treated according to standard medical care as covered by National Health Insurance.

Sample size estimation

Sample size and power considerations are based on the primary outcome of the number of conversations about age-related concerns. In our preliminary study (unpublished data) of 40 Japanese elderly cancer patients, the number of age-related concerns discussed during their consultations was 1.4 in the usual care arm and 2.3 in the

intervention arm (*SD* 1.3). Along with the results of a previous study on communication in Japanese cancer patients,[18] we defined the clinically minimally important difference in the number of age-related conversations as 1.0. The design has 80% power with a significance level of 0.05 (two-sided) to detect a difference of 1.0 in the number of conversations about age-related concerns with an *SD* of 2.5. Assuming a 5% withdrawal rate, 210 is the targeted accrual.

Statistical Analysis

In accordance with intention-to-treat principles, the primary outcome will be analyzed to examine the intervention effect parameters for all randomly assigned subjects. To compare categorical variables, Fisher's exact tests will be used. Continuous measures will be compared using the Wilcoxon rank-sum test. Overall survival and treatment failure free survival will be estimated using the Kaplan–Meier method and compared using log-rank test. No interim analysis is planned.

Patient and public involvement statement

This study protocol was co-designed by a cancer patient and family member of a pancreatic cancer patient, and it was reviewed by patient and public involvement (PPI)

representatives. PPI representatives will help our team disseminate the results of this study. The QPL was reviewed and revised based on comments from elderly cancer patients who were treated at the National Cancer Center in Tokyo.

Data management, central monitoring, data monitoring, and auditing

Except for audio-recorded data, all data will be collected through electronic data capture (EDC) and electronic-patient reported outcomes (ePRO) systems. Paper questionnaires will be used for patients with physical or cognitive limitations. Data management and central monitoring will be performed by the J-SUPPORT Data Science Team using EDC Viedoc™ (Viedoc Technologies AB, Uppsala, Sweden). No auditing is planned for this study.

Publication policy

The protocol and study results will be submitted to peer-reviewed journals. The first author of the main paper should be a member of the steering committee. The list of coauthors will be determined prior to submission of each paper.

Ethics and dissemination

This study will be conducted in accordance with the ethical guidelines for

clinical studies published by the Japanese Ministry of Education, Science and Technology and the Ministry of Health, Labour and Welfare, the modified Act on the Protection of Personal Information, and the ethical principles for research on human subjects stipulated in the Declaration of Helsinki and its amendments. If important protocol modifications are necessary, the investigators will discuss and report them to the review committee for approval. With regard to dissemination, the results obtained will be submitted to peer-reviewed journals. The main and relevant findings will be presented at conferences.

DISCUSSION

Our intervention program is unique in combining a GA summary and management recommendations with communication support using a QPL. Several randomized controlled trials in the United States have demonstrated the efficacy of GA and GA-guided management for elderly cancer patients.[10 11 27] There seems to be two core components of GA-guided management among these trials: (1) stratifying elderly cancer patients based on GA results in order to select appropriate treatment and (2) intervening in impaired GA domains with a multidisciplinary team.[31] This study focuses on GA-guided management by a multidisciplinary team. In prior studies, limited implementation of GA management recommendations did not improve patient outcomes, even when GA

results and management recommendations were presented to attending oncologists.[44 45] No data exist on whether an increased number of age-related conversations will improve QOL, maintain physical function, decrease treatment-related toxicities, and prolong patient survival. However, we chose the number of age-related conversations as the primary outcome for this study because GA-guided management will not be implemented in daily oncology practice, and thus not lead to the improvement of patient outcomes, unless these problems are well recognized and shared between patients and their oncologists.

In this study, trained intervention providers will perform the GA+QPL intervention in an interview format over 30–40 min. For future implementation of the intervention program, in addition to the study's web-based system on a touch-panel screen, electronic media such as AI-navigated self-administered GA and communication support might be more applicable to reducing burdens of time and human resources.

Study strengths and limitations

This study has three methodological limitations. First, due to the nature of the intervention, both patients and their oncologists would be aware of the allocated arm, which could potentially influence care during treatment. Second, because the intervention

program is complex and consists of multi-factorial components, each component's contribution to the outcomes would be hard to ascertain. Third, because this study is limited to patients with gastrointestinal cancers, its generalizability to other cancers will not be clarified.

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Author Contributions

MF is the principal investigator. AM is the project manager. MF, AM, NB, AT, TO, YM, FN, and YU developed the intervention program, including the QPL, the GA summary, and management recommendations. MF, AM, NB, AT, KM, TA, TS, AO, TM, YM, FN, and YU participated in the study design. All authors prepared the protocol and agree with the final protocol and revisions. KM played a chief role in developing the

statistical parts. AO and TM played roles in the data management. MF and AM drafted the manuscript. All authors participated in, read, and approved the final manuscript.

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Sponsor

None.

Competing interests

All authors declare that they have no competing interests regarding this work. NB reports grant from Ono Pharmaceutical and Takeda Pharmaceutical, and personal fees from Ono Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, and Daiichi Sankyo. TO reports grant from AstraZeneka, Bristol-Myers Squibb, MSD, Eisai, Syneos Health, EP-CRSU, and Incyte, and personal fees from AstraZeneka, MSD, Incyte, Eisai,

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GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

Patient consent for publication

Not required.

Ethics approval

The protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center on April 15, 2021 (ID: 2020-592) as well as by the J-SUPPORT Scientific Advisory Board. The patient consent form is attached to this submission as Appendix A.

Provenance and peer review

Not commissioned; externally peer reviewed.

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GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

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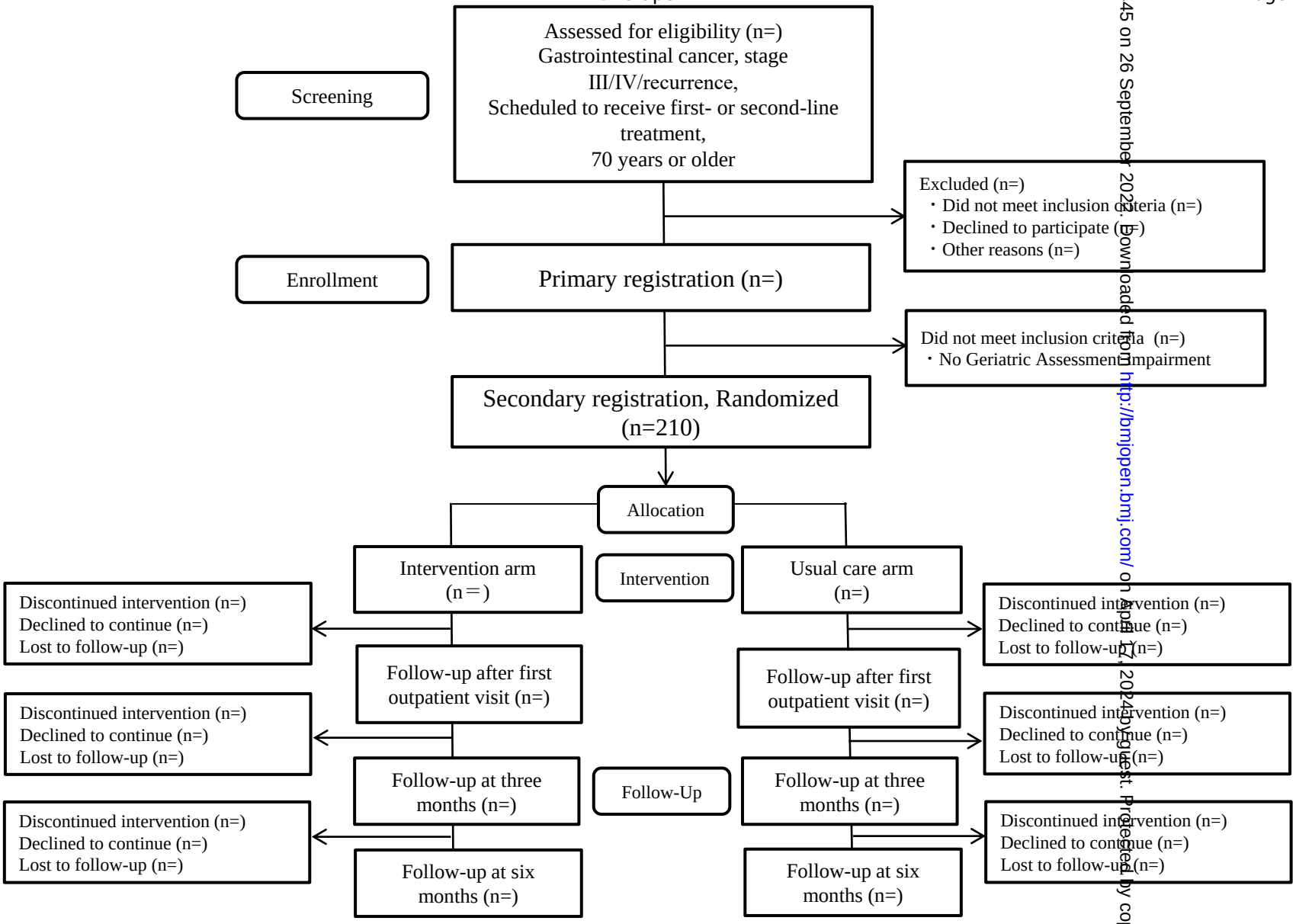

Figure 1. Flow diagram

Appendix A: Informed Consent Form for Patients

高齢がん患者さんのニーズにあった治療選択・治療継続のための包括的機能評価とコミュニケーション支援に関する研究のお願い

正式な研究課題名：高齢進行・再発がん患者のニーズに即した治療選択・継続のためのアプリケーションを活用した高齢者機能評価とマネジメント強化による支援プログラム開発

＜本説明同意文書のまとめ＞

- この説明文書は、臨床研究の内容について説明するものであり、研究対象者の候補となる方が臨床研究の参加について検討する上で、研究者の説明を補い、この研究の内容を理解して、参加するかどうかを考えていただくために用意しました。必ず研究者から説明を聞いていただき、わからないことなどがありましたら研究者に遠慮なくご質問ください。
- この臨床研究に参加するかどうかは、あなた自身の考えで決めることができます。くわしく知りたい場合は、研究計画書を閲覧することもできます。なお、この研究に参加しない場合でも、あなたはなんら不利益を受けません。
- 今回私たちは、高齢患者さんの身体・心理機能や社会生活の状況を適切に評価したうえで必要なサポートを提案し、加齢に伴う治療や生活の心配事について医師と話し合うことで、より患者さんのニーズに合った治療選択や治療継続につながると考えて、この研究を計画しました。
- 研究の目的は、①加齢に伴って生じる体や心、生活の変化について評価し、治療への影響が少なくなるように定期的にサポートすることに加え、②加齢に伴う治療や療養上の心配事を患者さんと医師とで共有することが、診察時のコミュニケーションをより良くするかを確認することです。
- 研究の対象となる方は、消化器（食道・胃・大腸・肝・胆・膵）のがんと診断され、70歳以上の方で、新たに化学療法を受ける、もしくはお薬を変更する予定の方です。
- 新しい取り組みでは、患者さんの身体・心理機能や社会生活の状況について、アンケート調査を行い、結果に基づいて必要なサポートを個別に提案します。さらに加齢に伴う心配事について、医師と相談できるよう質問支援をします。

1. 臨床研究とこの説明文書について

病気の診断や治療の方法の開発のためには多くの研究が必要です。現在行われている診断や治療の方法も長い時間をかけて研究され、進歩してきました。

国立がん研究センターも、がん医療の発展に貢献するため、さまざまな研究に積極的に取り組んでいます。こうした研究の中でも、患者さんにご協力いただいて行うものを、「臨床研究」といいます。臨床研究は、皆様のご理解とご協力によって初めて成り立つものであり、現在ある治療法もこれまで研究に参加してくださった多くの方々のご協力の結果によるものです。

この臨床研究を実施するにあたっては、患者さんの人権や安全への配慮について、医学の発展に役立つかどうかについて国立がん研究センター研究倫理審査委員会で審査され、承認を受け、理事長の許可を受けています。また、その際、国の定めた倫理指針に従って計画された研究であることも審査されています。

この説明文書は、臨床研究の内容について説明するものであり、研究対象者の候補となる方が臨床研究の参加について検討する上で、研究者の説明を補い、この研究の内容を理解して、参加するかどうかを考えていただくために用意しました。必ず研究者から説明を聞いていただき、わからないことなどがありましたら研究者に遠慮なくご質問ください。

2. 参加の自由について

この臨床研究に参加するかどうかは、あなた自身の考えで決めることができます。

この臨床研究についてさらにくわしく知りたい場合は、研究の実施に支障のない範囲で研究計画書を閲覧することもできますので、研究者にお尋ねください。

なお、この研究に参加しない場合でも、通常通りの治療を受けることは保証され、あなたが不利益を受けることはありません。また、研究の参加に同意したあとでも、いつでも、またどんな理由でも研究参加をとりやめることができます。その場合も、不利益を受けることはありません。

これから、この臨床研究についての詳しい説明をお読みになり、また、研究者からの説明を受け、臨床研究の内容を理解し、参加を希望する場合は、研究の説明者に同意する旨をお伝えください。

3. この臨床研究の対象となる方

この研究では、進行・再発期の消化器がん（食道がん、胃がん、大腸がん、肝臓がん、胆道がん、膵臓がんを含みます）と診断され、70歳以上の方で、新たに化学療法を受けることになった、もしくは化学療法のお薬を変更する予定の患者さんを対象とします。

研究に参加し、最初に実施するアンケート（高齢者機能評価）で、体や心の機能、社会生活の状況の評価において問題がなかった場合には、その後のアンケートや面談の対象にはなりません（化学療法の有害事象について、3 か月後、6 か月後のカルテ調査のみ行います）。

4. この臨床研究の意義と目的について

70歳以上の患者さんの化学療法では、患者さんの年齢を考慮して、体や心の機能や社会生活の状況を確認したうえで、患者さんの価値観も考慮した、より良い治療を患者さんと相談して決めることが勧められています。高齢がん患者さんには、ご自分の意向を医師に伝えることに不安を持っている方もおられるため、本研究では面談を行い、ご意向に即した内容を医師に質問できるように支援させていただきます。

今回私たちは、新しい診察の方法として、アプリケーションを用いたアンケート（高齢者機能評価）を実施することで、患者さんの体や心の機能や社会生活の状況を確認し、加齢による治療への影響を軽減するための支援をすすめるとともに、パンフレットを用いた面談によってコミュニケーション支援を実施すると、患者さんと医師との話し合いがより良くなるか、ということを調べるために研究を計画しました。本研究により、より安全で有効な治療を受けることができる可能性があります。

また、最初に実施する、体や心の機能、社会生活の状況についてのアンケート（高齢者機能評価）と、化学療法の有害事象との関連についても検討させていただきます。

5. この臨床研究の方法

「図. 研究の概要について」をご参照ください。研究に参加される場合、患者さんの体や心の機能や社会生活の状況についてアンケート（高齢者機能評価）への回答をお願いします。アンケートはアプリケーションを用いて入力し、回答にかかる時間はおよそ 10～20 分です。このアンケート（高齢者機能評価）で、体や心の機能、社会状況の評価でサポートが提案されなかった場合には、その後の面談やアンケート、診察録音の対象にはなりません。化学療法の有害事象について、3 か月後、6 か月後のカルテ調査のみ実施させていただきます。

最初に実施するアンケート（高齢者機能評価）で何らかのサポートが提案された患者さんは、診察時の様子を知るために診察を一度、録音をさせていただきます。そのほかに治療に関連する診療記録を研究調査員がカルテから確認させていただきます。カルテから確認する情報は、診断名、診断されたがんの特徴（進行度・深達度・組織型の分類）、治療内容、治療に伴う症状の程度、介護保険、診療報酬明細書などの情報です。また、これらの情報について、もしも転院された場合には、医師の許可を得て転院先の病院に問い合わせを行うことがあります。

一部の方（新しい診察グループ）には、事前に介入マニュアルに基づいた研修を修了した介入者が面談させていただきます。面談は、診察の待ち時間や治療の合間に、初回は 30～40 分程度、2 回目以降は 10～20 分程度で行わせていただきます。ご同意を得られた場合のみ、面談を録音させていただきます。その際アプリケーションを用いて入力したアンケートをもとに個別に作成したパンフレットを用いて、体や心の状況と治療との関係について情報提供をいたします。また、体や心の状況に応じて、加齢による治療への影響を軽減するために、具体的にどのようなサポートを受けることができるかを提案します。この情報は医師にも共有いたします。さらに、新しい診察グループでは、加齢による治療への影響を軽減するためのサポートの実施状況について、面談または電話にて確認させていただきます。

その他の方（通常の診察グループ）には面談は行われません。どちらのグループになるか

は、あなた自身の希望や医師の判断ではなく「ランダム化」という方法で、コンピュータで無作為に割り付けして決まります。この方法は調べたい支援方法以外の条件（年齢、身体や病気の状態など）をほぼ同じにしたグループに分けて比べることで調べたい支援方法が本当によいかどうかを比べることができるため、もっとも科学的で良い方法とされています。どちらのグループも医師と治療について話し合いますし、ソーシャルワーカーや看護師、心理師等の相談外来の利用は、いつでもあなたの意向で自由に決めることができます。また通常の診察グループに入った場合にも、ご希望があれば、調査期間の終了後になりますが、新しい診察グループで使用するパンフレットをお渡しします。

具体的なスケジュールについて

面談の実施について、新しい診察グループでは面談を研究参加の診察時、その 3 か月後の診察時に計 2 回行います。さらに、新しい診察グループでは、1 か月毎に、近況の確認と治療の影響を軽減するためのケアの実施状況について、面談または電話で確認させていただきます。面談の時間調整のために、電話をさせていただく可能性があります。通常の診察グループでは面談はありません。またアンケートの実施について、両方のグループとも、研究参加の診察時、その 3 か月後と 6 か月後の診察時、計 3 回行います。転院された場合など、アンケートを郵送させていただく可能性があります。12 か月後の診察時には、研究者によるカルテ調査のみ行います。

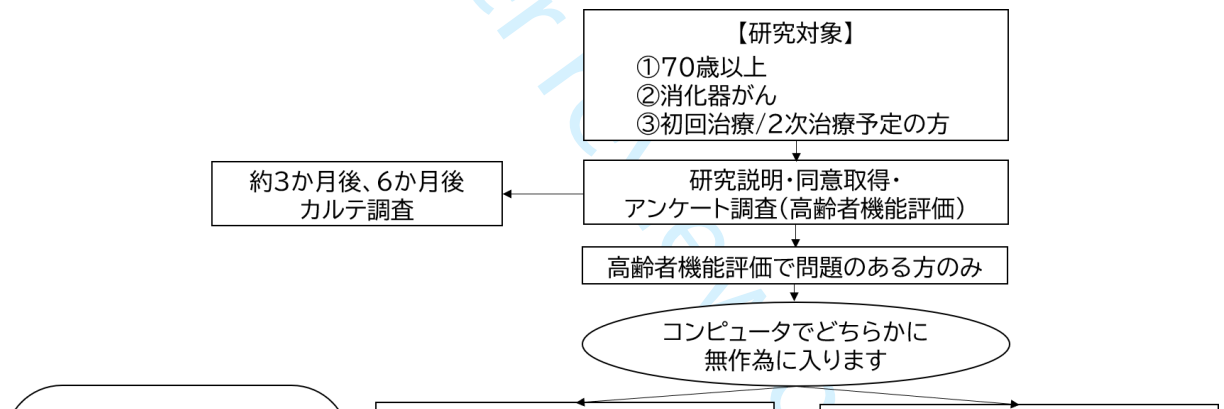

図. 研究の概要について

6. 研究参加により予想される利益と不利益

本研究へ参加することにより、新しい取り組みによる診察をうけた患者さんは、医師との

コミュニケーションが促進され、病気や治療に関する理解が増したり、長期的には不安が軽減したりといった利益を得る可能性があります。また、体や心の状況に応じたサポートを受けることで、加齢による治療への影響が軽減され、より安全で有効な治療が継続できる可能性があります。ただし、研究に参加することの不利益として、時間的な拘束の可能性があります。新しい取り組みによる診察として、初回はアンケートへの回答と面談で 40 分から 1 時間程度要します。2 回目以降は 20～30 分程度になります。外来での待ち時間や、治療中の患者さんが都合の良いときに実施するなど最大限に配慮します。

通常診察の患者さんは、本研究へ参加することによる利益はないと考えます。しかし新しい支援方法の確立に貢献することができます。一方で、アンケートへの回答として 10～20 分程度の時間を要します。

研究参加によって不都合が生じたり、対応が難しかったりする場合には担当スタッフや研究者まで遠慮なくお伝えください。

7. この臨床研究に参加しない場合の治療や支援について

この臨床研究に参加しない場合にも、あなたにとって最も適切だと思われる治療や支援が行われます。研究に参加しない場合にも、医師と治療について話し合うことはできますし、通常の診察同様に、心理師やソーシャルワーカーなどがいる相談外来を利用することは、いつでもあなたの意向で自由に決めることができます。

8. 臨床研究全体の実施予定期間

この臨床研究に参加される患者さんの研究登録期間は、研究が許可された日から 3 年間を予定しており、参加された患者さんの追跡期間は登録が終了してから 1 年間です。

研究全体の期間は研究が許可された日から 5 年間の予定です。

9. 費用負担と謝礼の支払いについて

この臨床研究に参加することに伴って必要になる、その他の診察や検査については健康保険が適用されますが、通常の治療を受ける場合と同じように自己負担分をお支払いいただくことになります。また研究参加に伴う謝礼はありません。

10. 健康被害が発生した場合の対応・補償について

この臨床研究は、アンケートと面談による支援であり、予測できなかった重い副作用などの健康被害が生じることは想定されません。

11. 個人情報の保護について

この臨床研究に参加すると、個人情報と診療情報に関する記録の一部は、研究事務局である国立がん研究センターがん対策研究所と、データセンターである中央病院支持療法部門内に保管され、研究代表者が責任を持って管理します。臨床研究で使用するデータ管理のため

に収集する情報には、カルテ番号、生年月日、その他(年齢、性別、がん種、進行期、治療レジメン)が含まれます。また、アンケートの郵送や、電話連絡のために、氏名、住所、電話番号を個人情報として取得させていただく可能性があります。

研究事務局と病院とのやり取りの際には、あなたのお名前ではなく研究で個別につけた研究番号を使用します。この固有の研究番号は、その後に行われる調査の際、医師が転勤した場合でも、臨床研究に参加していただいているあなたの情報を適切に管理するために、大変重要な情報となります。

研究に携わる研究者のうちデータ解析担当者に対して、個人情報を含まないデータを適切な管理の下で情報提供することがあります。提供する情報は、診断・治療に関する情報とアンケート結果を含みます。

【この臨床研究のデータ解析担当者】

静岡がんセンター臨床試験支援センター　統計解析室　室長:盛啓太

臨床試験の個人情報保護方法や管理について、国立がん研究センター研究倫理審査委員会の許可を得ています。研究事務局と共同研究施設では、これらの情報が外部にもれたり、臨床研究の目的以外に使われたりしない様、最大の努力をしています。この臨床研究にご参加いただける場合は、これらの個人情報の使用につきましてご了承くださいますようお願い申し上げます。

この研究が適切に行われているかどうかを第三者の立場で確認するために、当センター臨床研究監査を担当する部門の者などがあなたのカルテやその他の診療記録などを拝見することがあります。このような場合でも、これらの関係者には、守秘義務があり、あなたの個人情報は守られます。

12. データの二次利用について

この臨床研究で得られた情報を二次利用することがあります。この場合は、個人を識別する情報を結びつかないように匿名化した上、がん患者さんの生活の質の向上に役立てる目的に限り、データを利用いたします。

13. 試料・情報の取扱いについて

この臨床研究で得た情報は、研究者の所属する研究機関のルールに従い、研究終了報告書提出日から５年、あるいは、本研究に関連したあらゆる論文の公表日から３年のいずれか遅い日まで保管いたします。これは現在、研究結果を他の誰かがあとから検証できるようにするためには必要な措置だと考えられています。なお、定められた期間が過ぎ、廃棄が必要になった場合は、それらが誰のものか直ちにわからないよう加工した後に廃棄させて頂きます。音声録音データも含めた電子媒体はデータを完全削除し、紙媒体はシュレッダーにかけて廃棄いたします。

14. この臨床研究の結果の公表と返却について

この臨床研究から得られた結果は、医学関係の学会や医学雑誌などで公表いたします。発表に際しあなたのお名前など個人を特定できる情報を使用することはありません。

なお、この臨床研究の解析結果は研究段階のものであり、原則としてあなたにお伝えすることはありません。ただし、もしもそれらの情報があなたの健康状態にとって有用である可能性が高まった場合には、専門家や医師と慎重に協議した上で、あらためて医師からご連絡を差し上げることがあります。この臨床試験に関する情報については、定められた規定に従って、大学病院医療情報ネットワーク臨床試験登録システム（UMIN-CTR）【https://www.umin.ac.jp/ctr/index-j.htm】に登録し、公開いたします。

15. この臨床研究の資金と利益相反について

1)「利益相反」の説明

臨床研究における利益相反とは、研究者が企業等から経済的な利益（謝金、研究費、株式等）の提供を受け、その利益の存在により臨床研究の結果に影響を及ぼす可能性がある状況のことをいいます。

2)利益相反の有無および内容説明に関する記載

本研究は、国立研究開発法人日本医療研究開発機構　令和３年度革新的がん医療実用化研究事業　領域６（研究代表者：藤森麻衣子、課題管理番号 21ck0106682h0001）を資金源として実施します。この他に、特定の団体からの資金提供や薬剤等の無償提供などは受けておりませんので、研究組織全体に関して起こりうる利益相反はありません。

3)利益相反の管理方法に関する記載

研究者の利益相反の管理は、参加施設それぞれが自施設の研究者に関して行っています。当センターの研究者の利益相反の管理は国立がん研究センター利益相反委員会が行っていますので、詳細をお知りになりたい場合は、医師までお問い合わせください。

16. 研究組織・連絡先

この臨床研究について何か知りたいことや、何か心配なことがある場合や、同意を撤回したい場合、遠慮なくおたずね下さい。また、臨床研究終了後の結果についてお知りになりたい方も、研究事務局におたずね下さい。対応時間は平日９～17時です。

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共同研究者

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静岡がんセンター臨床試験支援センター 統計解析室 室長：盛啓太
杏林大学医学部附属病院 腫瘍内科学 教授：長島文夫

ご本人保管用/診療録保管用

同 意 文 書

国立がん研究センター中央病院　病院長　殿

研究課題名：高齢進行・再発がん患者のニーズに即した治療選択・継続のためのアプリケーションを活用した高齢者機能評価とマネジメント強化による支援プログラム開発

1. 臨床研究とこの説明文書について
2. 参加の自由について
3. この臨床研究の対象となる方
4. この臨床研究の意義と目的について
5. この臨床研究の方法
6. 研究参加により予想される利益と不利益
7. この臨床研究に参加しない場合の治療や支援について
8. 臨床研究全体の実施予定期間
9. 費用負担と謝礼の支払いについて
10. 健康被害が発生した場合の対応・補償について
11. 個人情報の保護について
12. データの二次利用について
13. 試料・情報の取扱いについて
14. この臨床研究の結果の公表と返却について
15. この臨床研究の資金と利益相反について
16. 研究組織・連絡先

私は、本臨床研究について以上の項目を説明しました。

説明日：　令和　　年　　月　　日

説明者氏名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿（自署）

私はこの研究に参加するにあたり、研究の内容について担当者より十分な説明を受けました。研究の内容を理解しましたので、参加することについて同意します。

同意日：　令和　　年　　月　　日

氏名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿（自署）

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill8W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	7
Funding	#4	Sources and types of financial, material, and other support	28
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	28
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	29
Roles and responsibilities: sponsor and funder	#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	28
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	9-11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9-11
Objectives	#7	Specific objectives or hypotheses	11
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, non-inferiority, exploratory)	12
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	12

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)	13
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-18
Interventions: modifications	#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)	19
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18
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	19-22

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)	14
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	23
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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	15
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	15

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection plan	#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	19

Data collection plan: retention	#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	19
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	24
Statistics: outcomes	#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	24
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24
Statistics: analysis population and missing data	#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)	24
Methods: Monitoring			
Data monitoring: formal committee	#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	24

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	24
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	22
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
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)	25

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	24
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
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	23
Dissemination policy: trial results	#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	25

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A
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	n/a

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Geriatric Assessment and Management with Question Prompt List using a Web-based Application for Elderly Cancer Patients (MAPLE) to Communicate Aging-related Concerns: J-SUPPORT 2101 study protocol for a multicenter, parallel group, randomized controlled trial

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GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

TITLE : Geriatric Assessment and Management with Question Prompt List using a Web-based Application for Elderly Cancer Patients (MAPLE) to Communicate Aging-related Concerns: J-SUPPORT 2101 study protocol for a multicenter, parallel group, randomized controlled trial

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GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

ABSTRACT (294 words)

Introduction

Elderly cancer patients often have aging-related physical and psychosocial problems that should be fully shared with their oncologists. Geriatric Assessment (GA) can assess these aging-related problems and guide management. Communication support might also facilitate implementation of GA-guided management. We will conduct a multicenter, randomized controlled trial to examine the efficacy of a program that combines a GA summary, management recommendations, and communication support to facilitate aging-related communications between elderly Japanese cancer patients and their oncologists, and thus to implement program-guided management.

Methods and analysis

We plan to recruit a total of 210 patients aged ≥ 70 years, diagnosed with incurable cancers of gastrointestinal origin, and referred for first- or second-line chemotherapy. In the intervention arm, a summary of management recommendations based on a GA and Question Prompt List (QPL) will be provided to patients and shared with their oncologists at the first outpatient visit after randomization by trained intervention providers. For five months after the initial intervention, implementation of

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GA-guided management recommendations will be reviewed monthly with the patients and their oncologists to implement management as needed. The GA and QPL will be re-evaluated at three months, with a summary provided to patients and their oncologists. Those participants allocated to the usual care arm will receive usual oncology care. The primary endpoint is the number of conversations about aging-related concerns at the first outpatient visit after randomization.

Ethics and dissemination

This study was approved by the Institutional Review Board of the National Cancer Center Japan on April 15, 2021 (ID: 2020-592). Study findings will be disseminated through peer-reviewed journals and conference presentations.

Trial status

The study is currently recruiting participants and the enrollment period will end on March 31, 2024, with an expected follow-up date of March 31, 2026.

Trial registration number UMIN000045428.

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Key words: Communication, decision making, Geriatric Assessment, patient-centered care, patient-physician relationship, quality of life, Question Prompt List

GERIATRIC ASSESSMENT AND MANAGEMENT WITH QUESTION PROMPT LIST FOR ELDERLY CANCER PATIENTS (MAPLE)

ARTICLE SUMMARY

Trial registration: The protocol was registered on September 13, 2021 at the UMIN Clinical Trials Registry (Registration No. UMIN000045428).

Data statement: The study protocol, data definition tables, and dataset will be uploaded to the UMIN-Individual Case Data Repository at https://www.umin.ac.jp/icdr/index-j.html.

Protocol version: The protocol was updated to version 6.0 on January 17, 2022.

Strengths and limitations of this study:

- This is the protocol paper of a multicenter, randomized controlled trial to examine the efficacy of a program that combines a Geriatric Assessment (GA), GA-guided management, and communication support using a Question Prompt List (QPL) for elderly Japanese cancer patients.
- With the aim of facilitating future implementation, this study will use a self-reported GA and QPL administered via a web-based application to generate a GA summary, tailored recommendations, and patients' selected questions.
- Due to the nature of the intervention, both patients and their oncologists would be

aware of the allocated arm, which could potentially influence care during treatment.

- The intervention program is complex, consisting of a multifactorial component (GA summary, management recommendations, and communication support using QPL), making it difficult to determine each component's contribution to the outcomes.
- Because this study is limited to patients with gastrointestinal cancers, its generalizability to other cancers will not be clarified.

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INTRODUCTION

Many cancers are aging-related diseases[1]. Japan is a front-runner of the super-aged societies, which is defined as greater than 21% of a population aged ≥65 years[2], and its number of elderly cancer patients is increasing. In Japan, more than 70% of cancer incidences and 80% of cancer mortality occur in patients aged ≥65 years[3, 4]. However, elderly patients are often excluded from clinical trials and they face difficulty due to lack of evidence for treatment decisions[5]. Elderly cancer patients are physically, psychologically, and socially heterogeneous; they differ from their younger counterparts in terms of physical function, psychological well-being, life circumstances, and values and preferences[6]. Therefore, the treatment and care of elderly cancer patients is complex and should be individualized. Subjective assessment by oncologists based on performance status and chronological age is inadequate to cope with these heterogeneous conditions, which can lead to overtreatment or undertreatment. The concept of geriatrics, which evaluates elderly patients in a multifaceted and comprehensive manner, is necessary in oncology.

Comprehensive Geriatric Assessment (CGA) is a multidimensional, interdisciplinary diagnostic process that focuses on determining the medical, psychosocial, and functional capabilities of elderly adults in order to develop a

coordinated and integrated plan for treatment and long-term follow-up[7]. In geriatrics, CGA has been shown to reduce mortality, decrease institutionalization and readmission, and improve cognitive and physical functioning, mainly through interventions by a multidisciplinary team[8, 9]. The term "geriatric assessment" (GA) is commonly used in oncology instead of CGA because CGA research in oncology has studied mainly the diagnostic process for selecting appropriate treatment through assessment of aging-related problems without a thorough focus on geriatric interventions for these problems[10]. Recently published randomized controlled trials (RCTs) in the United States have demonstrated that feedback in the form of a GA summary and GA-guided management recommendations to patients and their oncologists facilitates communication about aging-related concerns (COACH study)[11], and reduces incidences of serious adverse events related to chemotherapy (GAP70+ study)[12].

Patient-centered communication is important to help patients prioritize their concerns, ensuring that decisions are in line with their values and preferences. Although studies have shown benefits of communication interventions to facilitate patient-centered communication[13, 14], these interventions were not tailored to address aging-related concerns of elderly cancer patients. In fact, many elderly cancer patients have aging-related symptoms that are not identified, communicated, or addressed in daily oncology

practice[15]. Communication interventions might help elderly cancer patients and their oncologists share and manage aging-related problems by recognizing these conditions that are often overlooked in daily oncology practice.

Elderly cancer patients in Japan are less likely to communicate their values and preferences regarding treatment to their physicians; therefore, they need support to express their intentions and preferences based on their values[16]. A Question Prompt List (QPL) is a list of specific questions that helps patients express their intentions by facilitating communication with their healthcare providers and encouraging them to ask their healthcare providers questions[17]. A systematic review has shown that use of a QPL increases the number of questions that patients ask their physicians[18]. We previously conducted an RCT on the usefulness of QPL in Japanese patients with advanced cancer undergoing initial anticancer therapy and found that patients perceived the materials, including the QPL, to be useful for understanding their treatment plans[19].

Although our study is based on the COACH study, we hypothesize that feedback in the form of only a GA summary and GA-guided management recommendations to patients and their oncologists would be insufficient for elderly cancer patients in Japan to express their aging-related concerns. We further hypothesize that they would need communication support to express their concerns about problems identified by GA as

well as their interest in GA-guided management recommendations. Therefore, this study will examine the efficacy of a program that combines a GA summary, GA-guided management recommendations as provided by a multidisciplinary team, and communication support using QPL, with the aims of facilitating communications between elderly cancer patients and their oncologists. The rationale for combining these two interventions is that, after GA identifies aging-related concerns not captured in routine oncology practice, with communication support using QPL, patients will be able to express their aging related-concerns to their oncologists, which will facilitate patient-centered communication, thereby leading to higher implementation of GA-guided management and improved patient outcomes (Figure 1).

METHODS and ANALYSIS

This protocol was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and SPIRIT PRO Extension Guidelines[20, 21].

Study design

This study is a single-blind (outcome assessor blind), parallel-group RCT

conducted at the National Cancer Center Hospital and Kyorin University Hospital. The study period is from April 2021 to March 2026; the registration period is from September 2021 to March 2024.

This study protocol was reviewed and approved by the protocol review committee of Japan Supportive, Palliative, and Psychosocial Oncology Group as a J-SUPPORT 2101 study and the institutional review boards at each participating institution.

Screening

Trained study staff will review a list of potentially eligible patients (Table 1) and approach patients consecutively with permission from their oncologists.

Table 1. Inclusion and exclusion criteria for patients and oncologists

Participant	Inclusion Criteria	Exclusion Criteria
Patient	(1) Diagnosis of esophageal, gastric, colorectal, hepatic, biliary tract, or pancreatic cancer (2) Incurable disease (locally advanced stage III, IV, or recurrent) (3) Age ≥70 years (4) ECOG Performance Status score of 0–2 (5) Scheduled to receive first- or second-line chemotherapy (6) Able to read, write, and understand Japanese (7) Provide written informed consent for trial participation	(1) Scheduled to undergo surgery within three months (2) Participating or planning to participate in other interventional studies for which intervention by this study would be undesirable (e.g., other psychological or communication support studies, clinical trials, etc.) (3) Judged to have difficulty participating in the study by

	(8) Have at least one impairment of GA domains other than polypharmacy at the time of registration	attending oncologists
Oncologist	(1) Currently in clinical practice at participating institutions (2) Oncologists that care for patients with esophageal, gastric, colorectal, hepatic, biliary tract, or pancreatic cancer (3) Not planning to leave the practice during the next six months	(1) Non-physicians and physicians who are not oncologists

All elderly cancer patients who meet inclusion criteria (1) through (7) will be registered, and screened for GA. Patients having any GA impairment other than polypharmacy will be randomly assigned to either the intervention arm or the usual care arm (Figure 2).

Geriatric Assessment

All participants will undergo a GA that evaluates eight domains (falls, functional status, psychological status, nutrition, social support, cognition, polypharmacy, and comorbidity) using electronic patient-reported measures at baseline (Table 2).

Table 2. Geriatric Assessment (GA) Tools

GA Domain	Assessment Tools	Cut-off Points
Falls	History of falls in the past 6 months	Any history of falls
Functional Status	The Instrumental Activities of Daily Living (IADL) subscale of the	Any IADL deficit

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	Multidimensional Functional Assessment Questionnaire; Older American Resources and Services (OARS)[22]	
Psychological Status	Patient Health Questionnaire-9[23]	≥5 points
Nutrition	Mini Nutritional Assessment[24, 25]	≤11 points
Social Support	Living status, assistance	Living alone and/or without any assistance
Cognition	Mini-Cog[26]	≤2 points
Polypharmacy	Number of medications	≥5 regularly scheduled prescriptions
Comorbidity	Charlson Comorbidity Index[27]	≥3 points

These selected assessment tools are based on the American Society of Clinical Oncology (ASCO) guidelines, Japan Clinical Oncology Group geriatric research policy, and previous clinical trials[12, 15, 28-31]. Once these GA measures are entered via a web-based application that was developed in a previous study[32] and customized for the present study, a GA summary and management recommendations tailored to each patient will be generated as a PDF. This summary will contain information on GA impairments and GA-guided management recommendations based on literature reviews, guidelines, previous clinical trials, and expert consensus[12, 15, 28-31, 33] (Table 3). All assessments, other than cognitive and comorbidity measures performed by the study staff, will be self-administered on a touchscreen tablet. The study staff will assist patients who cannot independently complete the assessment.

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Table 3. Geriatric Assessment-Guided Management Recommendations

GA Impairments	Recommendations
Any history of falls Any Instrumental Activities of Daily Living (IADL) deficit	1. Referral to physical therapy and/or occupational therapy 1-1. Strength and balance training; introduce home exercise program 1-2. Assist according to IADL disability 1-3. Provide support according to falling risk 2. Referral to medical social workers and/or nurses 2-1. Provide support according to IADL disability 2-2. Evaluate home safety, adjust environmental factors (fall prevention), and use nursing care services 3. Review falling risk due to polypharmacy and adjust medications as needed (referral to pharmacist)
Patient Health Questionnaire-9 ≧5	1. Referral to a psychologist and/or psychiatrist 1-1. Cognitive-behavioral therapy and pharmacotherapy 2. Referral to medical social workers and/or nurses 2-1. Referral to hospital-based psychological support services 2-2. Referral to local social activities (e.g., community comprehensive support center)
Mini Nutritional Assessment ≦11	1. Referral to a dietician 1-1. Assess nutritional status; provide nutritional guidance 1-2. Provide information materials and brochures 1-3. Provide information on nutritional supplements; prescribe nutritional supplements 2. Referral to social workers as needed (assistance with shopping and meal preparation)
Living alone and/or without any assistance	1. Referral to medical social workers and/or nurses 1-1. Apply for long-term care insurance; referral to community comprehensive support center 1-2, Referral to transportation services, home care/nursing care, and support group 1-3. Identify and establish key persons in case of anyone's absence
Mini-Cog ≦2	1. Referral to a cognitive specialist or memory clinic (psychiatrist or neurologist)

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	1-1. Evaluate decision-making ability and capacity to consent as needed 1-2. Counsel on risk of delirium; reduce medications at risk of delirium 2. Encourage family/caregivers to participate in consultation and treatment decisions 3. Reduce the number of medications or adjust dosage and administration (referral to a pharmacist)
≧ 5 medications Charlson Comorbidity Index ≧3	1. Referral to a pharmacist 1-1. Reduce the number of medications or adjust dosage and/or administration 1-2. Discontinue potentially inappropriate medications (PIMs) 2. Consult with nurses and/or a pharmacist to confirm adherence 2-1. Determine patient's understanding of medication, missed doses, and patient's ability to manage medications and decipher text on a medication bag 3. Involve family and caregiver in treatment decisions and management of comorbidities 4. Review prescriptions and management of comorbidities by family physicians, geriatricians, and other specialists

Note. GA = Geriatric Assessment.

Randomization

Participants will be randomly allocated (1:1) to an intervention arm or a usual care arm (Figure 2). Computer-generated random allocation sequences will be provided and centrally controlled by an independent data center. A stratified block-randomization method will be used to ensure balanced allocation by study site, cancer type (esophageal, gastric, colorectal, hepatic, biliary tract, or pancreatic), and line of treatment (first or second). Allocation results will be sent electronically to the study staff at each institution. Participants and their oncologists will remain unblinded due to the nature of the

interventions.

Intervention

GA summary and management recommendations

In the intervention arm, a GA summary and management recommendations will be presented to the patients and their oncologists at the first outpatient visit after randomization (Figure 2). An intervention provider will explain the GA summary to the patient and then discuss the patient's perceptions of the GA impairments, need for recommended management, resources available at each institution, and other specific issues. An intervention provider will prepare a feedback sheet based on information obtained from the patients, including aging-related concerns and their interest in the recommendations, to reduce oncologists' burden. An intervention provider will present QPL on aging-related concerns as needed, and the patients can select aging-related questions from QPL to ask their oncologists. Oncologists will have autonomy to incorporate into their practice whatever recommendations are deemed necessary. The multi-disciplinary team at each institution will implement management recommendations with referrals from an oncologist based on clinical judgement. An intervention provider may help implement management recommendations with an oncologist's approval.

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For five months after the initial intervention, an intervention provider will review and discuss implementation of GA-guided management recommendations monthly with the patients and their oncologists to implement management as needed. Three months after the initial intervention, the GA will undergo reevaluation, and an intervention provider will provide a GA summary, management recommendations, and a feedback sheet to the patients and their oncologists so that GA-guided recommendations can be modified and implemented as needed.

Oncologists will receive a 20-min lecture on how to most effectively utilize GA information in their clinical practice for elderly cancer patients. An in-person group lecture will be provided and include an overview of the usefulness of GA and GA-guided management in oncology.

Communication support using QPL

In this study, a QPL that was developed based on our previous studies[19, 34, 35] to support shared decision-making for treatment of elderly cancer patients will be used to facilitate communications with attending oncologists. The QPL consists of 75 questions categorized into eight topics and a free-writing section for other aging-related questions based on the opinions of elderly cancer patients, oncologists, and geriatricians

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(Table 4).

Table 4. Domains of Question Prompt List and sample questions

Domains	**Sample questions**
1. Diagnosis and disease stage	・May I ask again what the diagnosis is ?
2. Current and future treatment	・Do comorbidities affect treatment or are they made worse by treatment? ・What treatment options do other patients in my situation have?
3. Management of current and possible future symptoms	・Why do the symptoms I am experiencing now occur? How long will they last? ・What are the symptoms or side effects of treatment that may occur in the future?
4. Daily life activities	・Can I discuss long-term care insurance? ・I am concerned about meal preparation and shopping. Are there any services available in my community? ・Do I need to reduce the number of medication I usually take ? ・Can I discuss my lack of appetite, difficulty eating, and weight loss? ・I am concerned about future visits to the hospital. Can I discuss transportation service? ・I want to exercise to keep my fitness level up. Can you introduce me to an exercise program that I can do at home?

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5. Care and expected prognosis after standard treatment	・Can I discuss home care and long-term care for the future? ・Can I ask what my future prospects might be?
6. Needs of caregivers	・Can someone listen to my family's concerns and worries?
7. Psychological distress and management	・Can I discuss my concerns and worries? ・I am having trouble enjoying or maintaining interest in things I used to enjoy. Can I discuss this with someone?
8. Values	・Can I tell you what is important to me in choosing treatment and what I really want to prioritize or continue in my life?

Patient communication coaching using the QPL consists of three parts: (1) reading a list and selecting questions that the patient prefers to discuss with their oncologists, and prioritizing selected questions via a web-based application; (2) discussing the reasons for and background behind selecting the questions, and identifying difficult questions to ask; and (3) practicing asking their oncologists these questions. Patients are given a 14-page A4 size QPL brochure for reference after the intervention. An intervention provider will prepare a feedback sheet, including a list of selected questions rephrased in the patients' own words, if necessary, for patients to present to their oncologists before the first outpatient visit after randomization (Figure 2).

Three months after the initial intervention, an intervention provider will provide

communication support using QPL and a feedback sheet for patients to present to their oncologists along with their GA results.

Intervention providers will be clinical psychologists, nurses, physicians, or hospital staff who have participated in intensive training using an intervention manual. They will hold weekly meetings to review all intervention sessions with supervision by the primary investigator to maintain quality. Intervention providers do not need to have prior experience or training for patient-centered communication. Through our training program and periodic feedback, even lay hospital staff with little clinical experience will be able to provide the intervention with fidelity.

In the usual care arm, participants will receive usual oncology care. Participants and their oncologists will not receive GA results at the time of registration unless severe cognitive or psychological problems are revealed.

Concomitant treatments will not be restricted.

Stopping rules for participants

The protocol intervention will be discontinued under the following conditions: (1) the attending oncologists deem it necessary to discontinue the intervention; (2) the

patient requests discontinuation of the intervention; (3) the patient dies during the intervention period; (4) the patient's condition suddenly deteriorates after registration, (5) a protocol violation or ineligibility is discovered; or (6) the patient withdraws consent to participate. The investigator will report the reasons for the discontinuation of the intervention to the data center. Follow-up assessments, including questionnaires, will continue unless consent is withdrawn.

Assessment measures

Table 5 shows the schedule of outcome measurements.

Table 5. Schedule of Outcome Measurements

	Baseline	Primary registration	Secondary registration	First outpatient visit after GA	Three months	Six months	Twelve months
GA	○				●		
Patient Characteristics*		○					
Oncologist Characteristics**				△			
Number of aging-related conversations				◎			
Quality of aging-related conversations				◎			
RIAS[36] and SHARE[37]				◎			

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CARE-10[38, 39]				◎	◎	◎	
TiOS[40, 41]				◎			
CTCAE					◎		
Prevalence of dose modifications					◎		
Implementation of GA-guided management					◎	◎	
GA Evaluation		○					
QPL Evaluation				●			
GA+QPL Evaluation				△		△	
PRO-CTCAE[42-44]			◎		◎	◎	
IADL[22]			◎		◎	◎	
QOL[45, 46]			◎		◎	◎	
Overall survival rate						◎	◎

○ will be evaluated among all participants at the primary registration.

◎ will be evaluated among all participants after the secondary registration.

● will be evaluated among participants in the intervention arm.

△ will be evaluated among attending oncologists in the intervention arm.

*Patient Characteristics include age, gender, highest level of education, employment status, marital status, financial concerns, and self-rated health.

**Oncologist Characteristics include age, gender, years in practice, and years in oncology practice.

Note. CARE-10 = Consultation and Relational Empathy measure-10; CTCAE = Common Terminology Criteria for Adverse Events; IADL = Instrumental Activities of Daily Living; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QOL = Quality of Life; QPL = Question Prompt List; RIAS = Roter intention analysis system; SHARE = setting, how to deliver bad news, additional information, reassurance, and emotional support; TiOS = Trust in Oncologists Scale; and GA = Geriatric Assessment.

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Primary outcome measure

The primary outcome is the number of conversations about aging-related concerns during consultation, which is used to evaluate whether the intervention facilitates discussions between patients and their oncologists. At the first outpatient visit within four weeks from the baseline GA, the conversation between patients and their oncologist will be audio-recorded and transcribed verbatim. Based on the COACH study[28], a content analysis framework will be used to assess how to identify aging-related concerns and whether stated concerns are acknowledged and considered further by the oncologist (quality of discussion) and to determine whether acknowledged concerns motivate implementation of management recommendations. For each transcript, coding will be performed directly by two coders who have received extensive training and supervision by the principal investigator, are blind to the study hypotheses and the allocation, and are not involved in any other aspect of the study.

Secondary outcome measures

We will evaluate several health outcomes as secondary outcome measures. Our hypothesis is that the intervention will facilitate aging-related communication between patients and their oncologists (primary outcome, proximal outcome), thereby leading to

higher implementation of GA-guided management (intermediate outcome), which in turn will lead to improved patient health outcomes (Figure 1). We will also evaluate communication outcomes as proximal outcome measures.

Health outcomes

1. Overall survival rate at six and twelve months. Overall survival is defined as the time from randomization to death from any cause or last contact, whichever is earlier.

2. Treatment failure-free survival, which is defined as the time from randomization to treatment discontinuation for any cause or last contact, whichever is earlier.

3. Grade 3–5 chemotherapy-related treatment toxicity within three months evaluated according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events ver. 5.0 by physicians and/or nurses.

4. Prevalence of dose modification within three months (treatment modification, dose reduction, and/or discontinuation).

5. Unscheduled hospitalization and emergency department visits within three months.

6. Functional status using the OARS-IADL questionnaire[22] (electronic-patient reported outcomes [ePRO]) consisting of seven questions rated on a three-point Likert scale; the Japanese version was translated and validated by Ogawa et al (unpublished data).

7. Quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30-item version (QLQ-C30 Questionnaire)[45] (ePRO) consisting of 30 items, including functional scales (physical, role, cognitive, emotional, and social), global health and QOL scale, symptoms scale and/or items (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea), and financial impact; the Japanese version was validated by Kobayashi et al[46].

8. Core items (12 symptoms) of the NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system; the Japanese version[42-44] (ePRO) was linguistically and psychometrically validated by Kawaguchi and Miyaji et al[43, 44].

Communication outcomes

9. Patient-centered communication behaviors will be analyzed based on impression ratings by two blinded coders. The analysis will utilize audio-recorded oncology visits for all participants and assess the total score of the 27 SHARE categories: setting, how to deliver the bad news, additional information, and reassurance and emotional support[37]. In addition, patient-preferred communication behaviors will be analyzed using the 40

categories of the Roter intention analysis system (RIAS)[36].

10. Communication satisfaction using the Consultation and Relational Empathy measure[38, 39] (CARE-10) (ePRO) consisting of 10 items rated on a five-point Likert scale; the Japanese version was translated and validated by Aomatsu et al[38].

11. Trust in Oncologists Scale (TiOS)[40, 41] (ePRO) consisting of five items rated on a five-point Likert scale; the Japanese version was translated and validated by the authors (unpublished data).

Intermediate outcomes

12. The number of geriatric problems successfully addressed for participants in the intervention arm.

Other outcomes

13. Patients' assessment surveys on the burden and usefulness of the intervention including "Was it difficult to answer the (GA) questions?" "Did you feel burdened by the (GA) questions?" "Did you feel burdened by the intervention (GA + QPL)?" "Did you find the intervention (GA + QPL) helpful in organizing your thoughts?" and "Did the intervention (GA + QPL) help you talk with your doctor?"

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14. Oncologists' assessment surveys on the burden and usefulness of the intervention including "Was the intervention (GA + QPL) useful to you?" and "Did you feel burdened by the intervention (GA + QPL)?"

Secondary outcome measures 1-5, and 12 will be collected through medical charts, consulting the oncologists if needed. Secondary outcome measures 6-8, 10, 11, and 13 will be collected through ePRO using a touchscreen tablet. Secondary outcome measure 14 will be collected using a paper form for the convenience of attending oncologists.

Harms

No specific serious adverse events are anticipated for participants in this study. Patients will be subjected to time burdens of 30–40 min for the study intervention and 10–20 min for the GA as well as baseline and follow-up questionnaires. There is no direct financial cost associated with study participation, but we recognize that patients are donating their time to participate. Patients will not be compensated for their participation.

Compensation

If patients develop any unforeseen health issues due to study participation, they

will be adequately treated according to standard medical care as covered by National Health Insurance.

Sample size estimation

Sample size and power considerations are based on the primary outcome of the number of conversations about aging-related concerns. In our preliminary study (unpublished data) of 40 Japanese elderly cancer patients, the number of aging-related concerns discussed during their consultations was 1.4 in the usual care arm and 2.3 in the intervention arm (*SD* 1.3). Along with the results of a previous study on communication in Japanese cancer patients[19], we defined the clinically minimally important difference in the number of aging-related conversations as 1.0. The design has 80% power with a significance level of 0.05 (two-sided) to detect a difference of 1.0 in the number of conversations about aging-related concerns with an *SD* of 2.5. Assuming a 5% withdrawal rate, 210 is the targeted accrual.

Statistical Analysis

In accordance with intention-to-treat principles, the primary outcome will be analyzed to examine the intervention effect parameters for all randomly assigned subjects.

To compare categorical variables, Fisher's exact tests will be used. Continuous measures will be compared using the Wilcoxon rank-sum test. Overall survival and treatment failure-free survival will be estimated using the Kaplan–Meier method and compared using log-rank test. No interim analysis is planned.

Missing Data

Every effort will be made to facilitate participants' completion of questionnaires, but missing data will inevitably occur due to dropout. We will evaluate the patterns of missing data and associations of missingness with other available variables. Based on the missing at random (MAR) assumption, the parameter estimates from the mixed-model analyses should be unbiased. However, if the data are suspected of being missing not at random (MNAR), a sensitivity analysis using selection and/or pattern-mixture models will be performed to determine the impact on the results. If the estimates are similar to the ones obtained from the simpler analysis of only complete cases, we will report the complete-case analysis results.

Patient and public involvement statement

This study protocol was co-designed by a cancer patient and family member of

a pancreatic cancer patient, and was reviewed by patient and public involvement (PPI) representatives. PPI representatives will help our team disseminate the results of this study. The QPL was reviewed and revised based on comments from elderly cancer patients who were treated at the National Cancer Center in Tokyo.

Data management, central monitoring, data monitoring, and auditing

Except for audio-recorded data, all data will be collected through electronic data capture (EDC) and ePRO systems. Paper questionnaires will be used for patients with physical or cognitive limitations. Data management and central monitoring will be performed by the J-SUPPORT Data Science Team using EDC Viedoc™ (Viedoc Technologies AB, Uppsala, Sweden). No auditing is planned for this study.

Publication policy

The protocol and study results will be submitted to peer-reviewed journals. The first author of the main paper should be a member of the steering committee. The list of coauthors will be determined prior to submission of each paper.

Ethics and dissemination

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This study will be conducted in accordance with the ethical guidelines for clinical studies published by the Japanese Ministry of Education, Science and Technology and the Ministry of Health, Labour and Welfare, the modified Act on the Protection of Personal Information, and the ethical principles for research on human subjects stipulated in the Declaration of Helsinki and its amendments. If important protocol modifications are necessary, the investigators will discuss and report them to the review committee for approval. With regard to dissemination, the results obtained will be submitted to peer-reviewed journals. The main and relevant findings will be presented at conferences.

DISCUSSION

Our intervention program is unique in combining a GA summary and management recommendations with communication support using a QPL. Several RCTs in the United States have demonstrated the efficacy of GA and GA-guided management for elderly cancer patients[12, 28, 29]. There seems to be two core components of GA-guided management among these trials: (1) stratifying elderly cancer patients based on GA results in order to select appropriate treatment and (2) intervening in impaired GA domains with a multidisciplinary team[33]. This study focuses on GA-guided management by a multidisciplinary team. In prior studies, limited implementation of GA

management recommendations did not improve patient outcomes, even when GA results and management recommendations were presented to attending oncologists[47, 48]. To improve patient outcomes, it is necessary to successfully implement GA-guided management.

This study is expected to provide new evidence building on the COACH study, which demonstrated that feedback in the form of a GA summary and GA-guided management recommendations to patients and their oncologists facilitates communication about aging-related concerns[28]. Our study differs from the COACH study in the following ways: 1) an intervention provider will review and discuss GA results and GA-guided management recommendations with patients and then provide a feedback sheet based on information derived from the patients in order to reduce the oncologists' burden; 2) an intervention provider will provide communication support using QPL and help patients communicate aging-related concerns to their oncologists; and 3) an intervention provider will meet with the patients and oncologists monthly to review and facilitate implementation of GA-guided management as needed. We hypothesize that our intervention combining a GA summary and management recommendations with communication support using QPL will facilitate patient-centered communication about aging-related concerns, even among Japanese elderly cancer

patients who are less likely to express their values and preferences to their oncologists, thereby leading to successful implementation of GA-guided management. Previous studies in the United States have shown that older, non-White, lower-income, or less-educated patients tend to ask their physicians fewer questions, resulting in less effective communication[49-51]. Therefore, we believe that our intervention, if proven effective, would benefit not only Japanese elderly cancer patients but also other vulnerable populations who may be less likely to express their concerns to their oncologists, thereby contributing to reducing health-care disparities.

No data exist on whether an increased number of aging-related conversations will improve QOL, maintain physical function, decrease treatment-related toxicities, and prolong patient survival. However, we chose the number of aging-related conversations as the primary outcome for this study because GA-guided management will not be implemented in daily oncology practice, and thus not lead to the improvement of patient outcomes, unless these problems are well recognized and shared between patients and their oncologists.

In this study, trained intervention providers will perform the GA+QPL intervention in an interview format over 30–40 min. For future implementation of the intervention program, in addition to the study's web-based system on a touch-panel

screen, electronic media such as AI-navigated self-administered GA and communication support might be more applicable to reducing burdens of time and human resources.

Study strengths and limitations

The main strength of our study is that communication support using QPL is combined with GA. This approach is expected to facilitate patient-centered communication regarding aging-related concerns, even among vulnerable populations who are generally less likely to express their values and preferences to their oncologists. This study has three methodological limitations. First, due to the nature of the intervention, both patients and their oncologists would be aware of the allocated arm, which could potentially influence care during treatment. We have not chosen a cluster-randomized study design, so there might be a risk of contamination in that oncologists could learn from the intervention model and apply that knowledge to other patients given that they will be exposed to both arms. However, we consider this risk to be low because it is unlikely for oncologists to identify aging-related problems unless GA is performed; aging-related concerns are not captured by routine oncology assessments[15, 28]. Actually, GA is not performed in routine oncology practice at the participating institutions. Second, because the intervention program is complex and consists of multi-

factorial components, each component's contribution to the outcomes would be hard to ascertain. Third, because this study is limited to patients with gastrointestinal cancers, its generalizability to other cancers will not be clarified.

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Author Contributions

MF is the principal investigator. AM is the project manager. MF, AM, NB, AT, TO, YM, FN, and YU developed the intervention program, including the QPL, the GA summary, and management recommendations. MF, AM, NB, AT, KM, TA, TS, AO, TM, YM, FN, and YU participated in the study design. All authors prepared the protocol and agree with the final protocol and revisions. KM played a chief role in developing the statistical parts. AO and TM played roles in the data management. MF and AM drafted

the manuscript. All authors participated in, read, and approved the final manuscript.

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Sponsor

None.

Competing interests

All authors declare that they have no competing interests regarding this work. NB reports grant from Ono Pharmaceutical and Takeda Pharmaceutical, and personal fees from Ono Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, and Daiichi Sankyo. TO reports grant from AstraZeneca, Bristol-Myers Squibb, MSD, Eisai, Syneos Health, EP-CRSU, and Incyte, and personal fees from AstraZeneca, MSD, Incyte, Eisai, Taiho Pharmaceutical, Yakult Honsha, Ono Pharmaceutical, Pfizer, Daiichi Sankyo,

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Patient consent for publication

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Not required.

Ethics approval

The protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center on April 15, 2021 (ID: 2020-592) as well as by the J-SUPPORT Scientific Advisory Board. The patient consent form is attached to this submission as Appendix A, B.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure Captions.

Figure 1. Conceptual model of this study

In our conceptual model, GA will identify aging-related concerns not captured in routine oncology practice. Then, with communication support using QPL, patients will be able to express their aging-related concerns to their oncologists, which will facilitate patient-centered communication, thereby leading to higher implementation of GA-guided management and improved patient health outcomes.

Note. GA = Geriatric Assessment; QOL = Quality of Life; QPL = Question Prompt List

Figure 2. Flow diagram

Note. CARE-10 = Consultation and Relational Empathy measure-10; CTCAE = Common Terminology Criteria for Adverse Events; EORTC-QLQ-C-30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item version; ePRO = electronic-patient reported outcomes; GA = Geriatric Assessment; IADL = Instrumental Activities of Daily Living; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QOL = Quality of Life; QPL = Question Prompt List; RIAS = Roter intention analysis system; SHARE = setting, how to deliver bad news, additional information, reassurance, and emotional support; TiOS = Trust in Oncologists Scale

Figure 1. Conceptual model of the study

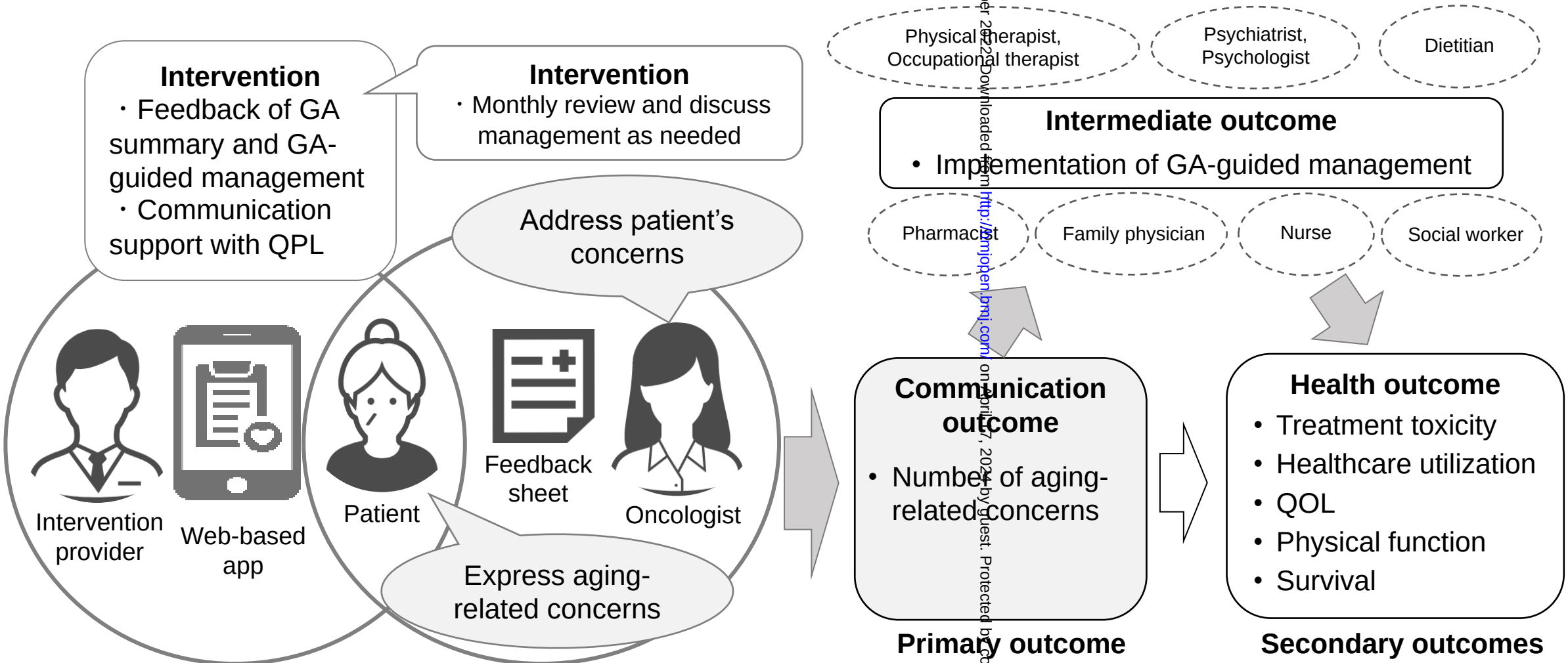
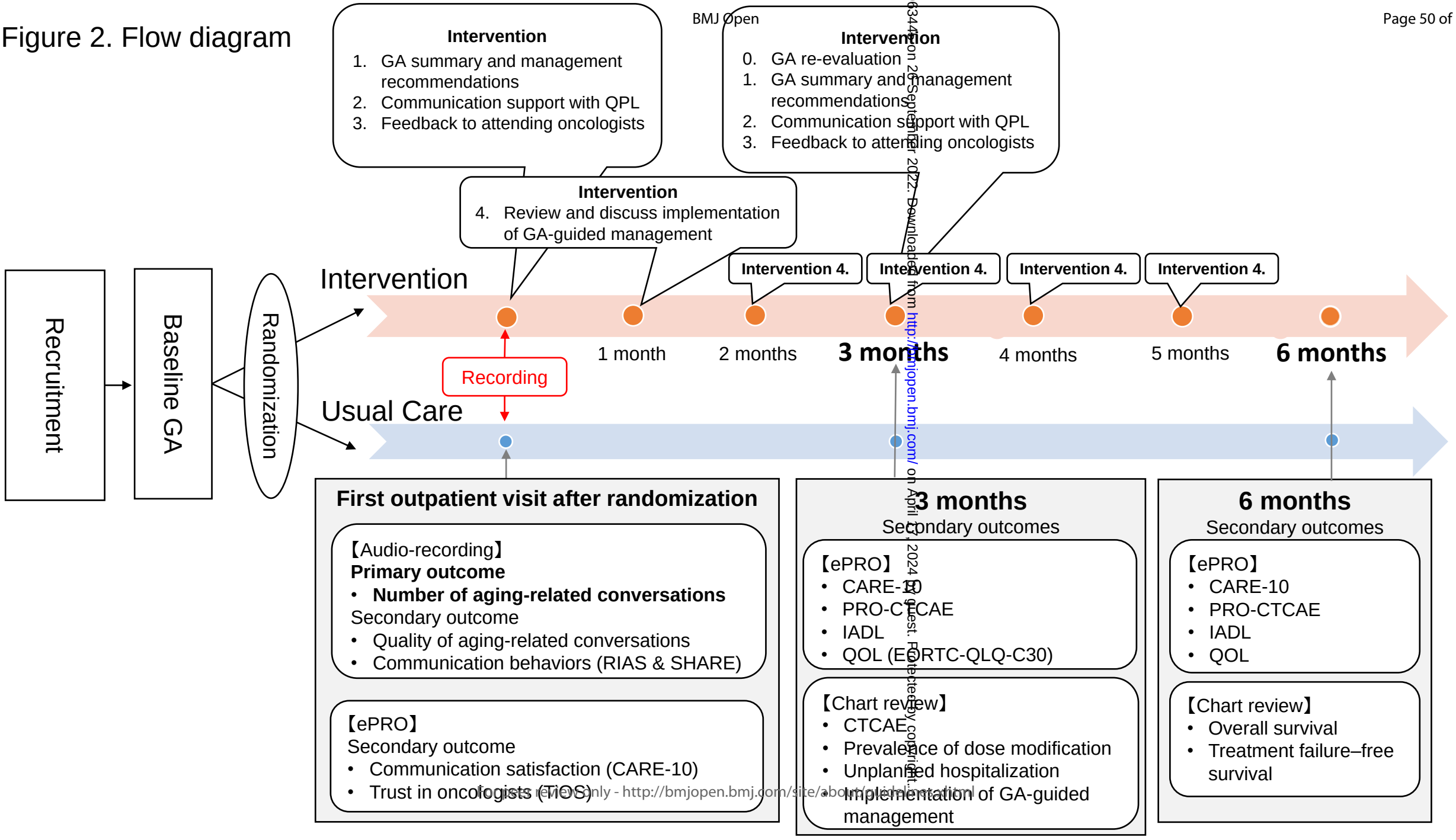


Figure 2. Flow diagram



Appendix A: Informed Consent Form for Patients

高齢がん患者さんのニーズにあった治療選択・治療継続のための包括的機能評価とコミュニケーション支援に関する研究のお願い

正式な研究課題名：高齢進行・再発がん患者のニーズに即した治療選択・継続のためのアプリケーションを活用した高齢者機能評価とマネジメント強化による支援プログラム開発

＜本説明同意文書のまとめ＞

- この説明文書は、臨床研究の内容について説明するものであり、研究対象者の候補となる方が臨床研究の参加について検討する上で、研究者の説明を補い、この研究の内容を理解して、参加するかどうかを考えていただくために用意しました。必ず研究者から説明を聞いていただき、わからないことなどがありましたら研究者に遠慮なくご質問ください。
- この臨床研究に参加するかどうかは、あなた自身の考えで決めることができます。くわしく知りたい場合は、研究計画書を閲覧することもできます。なお、この研究に参加しない場合でも、あなたはなんら不利益を受けません。
- 今回私たちは、高齢患者さんの身体・心理機能や社会生活の状況を適切に評価したうえで必要なサポートを提案し、加齢に伴う治療や生活の心配事について医師と話し合うことで、より患者さんのニーズに合った治療選択や治療継続につながると考えて、この研究を計画しました。
- 研究の目的は、①加齢に伴って生じる体や心、生活の変化について評価し、治療への影響が少なくなるように定期的にサポートすることに加え、②加齢に伴う治療や療養上の心配事を患者さんと医師とで共有することが、診察時のコミュニケーションをより良くするかを確認することです。
- 研究の対象となる方は、消化器（食道・胃・大腸・肝・胆・膵）のがんと診断され、70歳以上の方で、新たに化学療法を受ける、もしくはお薬を変更する予定の方です。
- 新しい取り組みでは、患者さんの身体・心理機能や社会生活の状況について、アンケート調査を行い、結果に基づいて必要なサポートを個別に提案します。さらに加齢に伴う心配事について、医師と相談できるよう質問支援をします。

1. 臨床研究とこの説明文書について

病気の診断や治療の方法の開発のためには多くの研究が必要です。現在行われている診断や治療の方法も長い時間をかけて研究され、進歩してきました。

国立がん研究センターも、がん医療の発展に貢献するため、さまざまな研究に積極的に取り組んでいます。こうした研究の中でも、患者さんにご協力いただいて行うものを、「臨床研究」といいます。臨床研究は、皆様のご理解とご協力によって初めて成り立つものであり、現在ある治療法もこれまで研究に参加してくださった多くの方々のご協力の結果によるものです。

この臨床研究を実施するにあたっては、患者さんの人権や安全への配慮について、医学の発展に役立つかどうかについて国立がん研究センター研究倫理審査委員会で審査され、承認を受け、理事長の許可を受けています。また、その際、国の定めた倫理指針に従って計画された研究であることも審査されています。

この説明文書は、臨床研究の内容について説明するものであり、研究対象者の候補となる方が臨床研究の参加について検討する上で、研究者の説明を補い、この研究の内容を理解して、参加するかどうかを考えていただくために用意しました。必ず研究者から説明を聞いていただき、わからないことなどがありましたら研究者に遠慮なくご質問ください。

2. 参加の自由について

この臨床研究に参加するかどうかは、あなた自身の考えで決めることができます。

この臨床研究についてさらにくわしく知りたい場合は、研究の実施に支障のない範囲で研究計画書を閲覧することもできますので、研究者にお尋ねください。

なお、この研究に参加しない場合でも、通常通りの治療を受けることは保証され、あなたが不利益を受けることはありません。また、研究の参加に同意したあとでも、いつでも、またどんな理由でも研究参加をとりやめることができます。その場合も、不利益を受けることはありません。

これから、この臨床研究についての詳しい説明をお読みになり、また、研究者からの説明を受け、臨床研究の内容を理解し、参加を希望する場合は、研究の説明者に同意する旨をお伝えください。

3. この臨床研究の対象となる方

この研究では、進行・再発期の消化器がん（食道がん、胃がん、大腸がん、肝臓がん、胆道がん、膵臓がんを含みます）と診断され、70歳以上の方で、新たに化学療法を受けることになった、もしくは化学療法のお薬を変更する予定の患者さんを対象とします。

研究に参加し、最初に実施するアンケート（高齢者機能評価）で、体や心の機能、社会生活の状況の評価において問題がなかった場合には、その後のアンケートや面談の対象にはなりません（化学療法の有害事象について、3 か月後、6 か月後のカルテ調査のみ行います）。

4. この臨床研究の意義と目的について

70歳以上の患者さんの化学療法では、患者さんの年齢を考慮して、体や心の機能や社会生活の状況を確認したうえで、患者さんの価値観も考慮した、より良い治療を患者さんと相談して決めることが勧められています。高齢がん患者さんには、ご自分の意向を医師に伝えることに不安を持っている方もおられるため、本研究では面談を行い、ご意向に即した内容を医師に質問できるように支援させていただきます。

今回私たちは、新しい診察の方法として、アプリケーションを用いたアンケート（高齢者機能評価）を実施することで、患者さんの体や心の機能や社会生活の状況を確認し、加齢による治療への影響を軽減するための支援をすすめるとともに、パンフレットを用いた面談によってコミュニケーション支援を実施すると、患者さんと医師との話し合いがより良くなるか、ということを調べるために研究を計画しました。本研究により、より安全で有効な治療を受けることができる可能性があります。

また、最初に実施する、体や心の機能、社会生活の状況についてのアンケート（高齢者機能評価）と、化学療法の有害事象との関連についても検討させていただきます。

5. この臨床研究の方法

「図. 研究の概要について」をご参照ください。研究に参加される場合、患者さんの体や心の機能や社会生活の状況についてアンケート（高齢者機能評価）への回答をお願いします。アンケートはアプリケーションを用いて入力し、回答にかかる時間はおよそ 10～20 分です。このアンケート（高齢者機能評価）で、体や心の機能、社会状況の評価でサポートが提案されなかった場合には、その後の面談やアンケート、診察録音の対象にはなりません。化学療法の有害事象について、3 か月後、6 か月後のカルテ調査のみ実施させていただきます。

最初に実施するアンケート（高齢者機能評価）で何らかのサポートが提案された患者さんは、診察時の様子を知るために診察を一度、録音をさせていただきます。そのほかに治療に関連する診療記録を研究調査員がカルテから確認させていただきます。カルテから確認する情報は、診断名、診断されたがんの特徴（進行度・深達度・組織型の分類）、治療内容、治療に伴う症状の程度、介護保険、診療報酬明細書などの情報です。また、これらの情報について、もしも転院された場合には、医師の許可を得て転院先の病院に問い合わせを行うことがあります。

一部の方（新しい診察グループ）には、事前に介入マニュアルに基づいた研修を修了した介入者が面談させていただきます。面談は、診察の待ち時間や治療の合間に、初回は 30～40 分程度、2 回目以降は 10～20 分程度で行わせていただきます。ご同意を得られた場合のみ、面談を録音させていただきます。その際アプリケーションを用いて入力したアンケートをもとに個別に作成したパンフレットを用いて、体や心の状況と治療との関係について情報提供をいたします。また、体や心の状況に応じて、加齢による治療への影響を軽減するために、具体的にどのようなサポートを受けることができるかを提案します。この情報は医師にも共有いたします。さらに、新しい診察グループでは、加齢による治療への影響を軽減するためのサポートの実施状況について、面談または電話にて確認させていただきます。

その他の方（通常の診察グループ）には面談は行われません。どちらのグループになるか

は、あなた自身の希望や医師の判断ではなく「ランダム化」という方法で、コンピュータで無作為に割り付けして決まります。この方法は調べたい支援方法以外の条件（年齢、身体や病気の状態など）をほぼ同じにしたグループに分けて比べることで調べたい支援方法が本当によいかどうかを比べることができるため、もっとも科学的で良い方法とされています。どちらのグループも医師と治療について話し合いますし、ソーシャルワーカーや看護師、心理師等の相談外来の利用は、いつでもあなたの意向で自由に決めることができます。また通常の診察グループに入った場合にも、ご希望があれば、調査期間の終了後になりますが、新しい診察グループで使用するパンフレットをお渡しします。

具体的なスケジュールについて

面談の実施について、新しい診察グループでは面談を研究参加の診察時、その 3 か月後の診察時に計 2 回行います。さらに、新しい診察グループでは、1 か月毎に、近況の確認と治療の影響を軽減するためのケアの実施状況について、面談または電話で確認させていただきます。面談の時間調整のために、電話をさせていただく可能性があります。通常の診察グループでは面談はありません。またアンケートの実施について、両方のグループとも、研究参加の診察時、その 3 か月後と 6 か月後の診察時、計 3 回行います。転院された場合など、アンケートを郵送させていただく可能性があります。12 か月後の診察時には、研究者によるカルテ調査のみ行います。

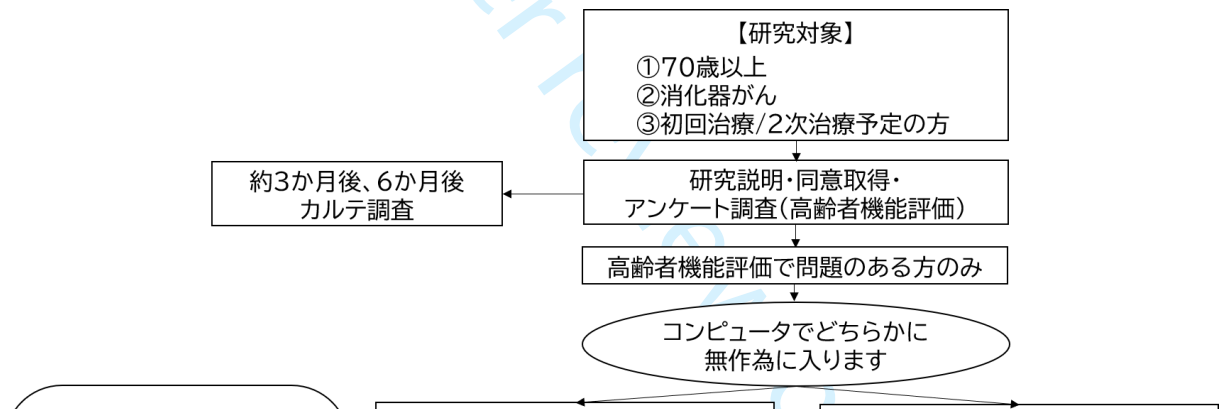


図. 研究の概要について

6. 研究参加により予想される利益と不利益

本研究へ参加することにより、新しい取り組みによる診察をうけた患者さんは、医師との

コミュニケーションが促進され、病気や治療に関する理解が増したり、長期的には不安が軽減したりといった利益を得る可能性があります。また、体や心の状況に応じたサポートを受けることで、加齢による治療への影響が軽減され、より安全で有効な治療が継続できる可能性があります。ただし、研究に参加することの不利益として、時間的な拘束の可能性があります。新しい取り組みによる診察として、初回はアンケートへの回答と面談で 40 分から 1 時間程度要します。2 回目以降は 20～30 分程度になります。外来での待ち時間や、治療中の患者さんが都合の良いときに実施するなど最大限に配慮します。

通常診察の患者さんは、本研究へ参加することによる利益はないと考えます。しかし新しい支援方法の確立に貢献することができます。一方で、アンケートへの回答として 10～20 分程度の時間を要します。

研究参加によって不都合が生じたり、対応が難しかったりする場合には担当スタッフや研究者まで遠慮なくお伝えください。

7. この臨床研究に参加しない場合の治療や支援について

この臨床研究に参加しない場合にも、あなたにとって最も適切だと思われる治療や支援が行われます。研究に参加しない場合にも、医師と治療について話し合うことはできますし、通常の診察同様に、心理師やソーシャルワーカーなどがいる相談外来を利用することは、いつでもあなたの意向で自由に決めることができます。

8. 臨床研究全体の実施予定期間

この臨床研究に参加される患者さんの研究登録期間は、研究が許可された日から 3 年間を予定しており、参加された患者さんの追跡期間は登録が終了してから 1 年間です。

研究全体の期間は研究が許可された日から 5 年間の予定です。

9. 費用負担と謝礼の支払いについて

この臨床研究に参加することに伴って必要になる、その他の診察や検査については健康保険が適用されますが、通常の治療を受ける場合と同じように自己負担分をお支払いいただくことになります。また研究参加に伴う謝礼はありません。

10. 健康被害が発生した場合の対応・補償について

この臨床研究は、アンケートと面談による支援であり、予測できなかった重い副作用などの健康被害が生じることは想定されません。

11. 個人情報の保護について

この臨床研究に参加すると、個人情報と診療情報に関する記録の一部は、研究事務局である国立がん研究センターがん対策研究所と、データセンターである中央病院支持療法部門内に保管され、研究代表者が責任を持って管理します。臨床研究で使用するデータ管理のため

に収集する情報には、カルテ番号、生年月日、その他(年齢、性別、がん種、進行期、治療レジメン)が含まれます。また、アンケートの郵送や、電話連絡のために、氏名、住所、電話番号を個人情報として取得させていただく可能性があります。

研究事務局と病院とのやり取りの際には、あなたのお名前ではなく研究で個別につけた研究番号を使用します。この固有の研究番号は、その後に行われる調査の際、医師が転勤した場合でも、臨床研究に参加していただいているあなたの情報を適切に管理するために、大変重要な情報となります。

研究に携わる研究者のうちデータ解析担当者に対して、個人情報を含まないデータを適切な管理の下で情報提供することがあります。提供する情報は、診断・治療に関する情報とアンケート結果を含みます。

【この臨床研究のデータ解析担当者】

静岡がんセンター臨床試験支援センター　統計解析室　室長:盛啓太

臨床試験の個人情報保護方法や管理について、国立がん研究センター研究倫理審査委員会の許可を得ています。研究事務局と共同研究施設では、これらの情報が外部にもれたり、臨床研究の目的以外に使われたりしない様、最大の努力をしています。この臨床研究にご参加いただける場合は、これらの個人情報の使用につきましてご了承くださいますようお願い申し上げます。

この研究が適切に行われているかどうかを第三者の立場で確認するために、当センター臨床研究監査を担当する部門の者などがあなたのカルテやその他の診療記録などを拝見することがあります。このような場合でも、これらの関係者には、守秘義務があり、あなたの個人情報は守られます。

12. データの二次利用について

この臨床研究で得られた情報を二次利用することがあります。この場合は、個人を識別する情報を結びつかないように匿名化した上、がん患者さんの生活の質の向上に役立てる目的に限り、データを利用いたします。

13. 試料・情報の取扱いについて

この臨床研究で得た情報は、研究者の所属する研究機関のルールに従い、研究終了報告書提出日から５年、あるいは、本研究に関連したあらゆる論文の公表日から３年のいずれか遅い日まで保管いたします。これは現在、研究結果を他の誰かがあとから検証できるようにするためには必要な措置だと考えられています。なお、定められた期間が過ぎ、廃棄が必要になった場合は、それらが誰のものか直ちにわからないよう加工した後に廃棄させて頂きます。音声録音データも含めた電子媒体はデータを完全削除し、紙媒体はシュレッダーにかけて廃棄いたします。

14. この臨床研究の結果の公表と返却について

この臨床研究から得られた結果は、医学関係の学会や医学雑誌などで公表いたします。発表に際しあなたのお名前など個人を特定できる情報を使用することはありません。

なお、この臨床研究の解析結果は研究段階のものであり、原則としてあなたにお伝えすることはありません。ただし、もしもそれらの情報があなたの健康状態にとって有用である可能性が高まった場合には、専門家や医師と慎重に協議した上で、あらためて医師からご連絡を差し上げることがあります。この臨床試験に関する情報については、定められた規定に従って、大学病院医療情報ネットワーク臨床試験登録システム（UMIN-CTR）【https://www.umin.ac.jp/ctr/index-j.htm】に登録し、公開いたします。

15. この臨床研究の資金と利益相反について

1)「利益相反」の説明

臨床研究における利益相反とは、研究者が企業等から経済的な利益（謝金、研究費、株式等）の提供を受け、その利益の存在により臨床研究の結果に影響を及ぼす可能性がある状況のことをいいます。

2)利益相反の有無および内容説明に関する記載

本研究は、国立研究開発法人日本医療研究開発機構　令和３年度革新的がん医療実用化研究事業　領域６（研究代表者：藤森麻衣子、課題管理番号 21ck0106682h0001）を資金源として実施します。この他に、特定の団体からの資金提供や薬剤等の無償提供などは受けておりませんので、研究組織全体に関して起こりうる利益相反はありません。

3)利益相反の管理方法に関する記載

研究者の利益相反の管理は、参加施設それぞれが自施設の研究者に関して行っています。当センターの研究者の利益相反の管理は国立がん研究センター利益相反委員会が行っていますので、詳細をお知りになりたい場合は、医師までお問い合わせください。

16. 研究組織・連絡先

この臨床研究について何か知りたいことや、何か心配なことがある場合や、同意を撤回したい場合、遠慮なくおたずね下さい。また、臨床研究終了後の結果についてお知りになりたい方も、研究事務局におたずね下さい。対応時間は平日９～17時です。

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ご本人保管用/診療録保管用

同 意 文 書

国立がん研究センター中央病院　病院長　殿

研究課題名：高齢進行・再発がん患者のニーズに即した治療選択・継続のためのアプリケーションを活用した高齢者機能評価とマネジメント強化による支援プログラム開発

1. 臨床研究とこの説明文書について
2. 参加の自由について
3. この臨床研究の対象となる方
4. この臨床研究の意義と目的について
5. この臨床研究の方法
6. 研究参加により予想される利益と不利益
7. この臨床研究に参加しない場合の治療や支援について
8. 臨床研究全体の実施予定期間
9. 費用負担と謝礼の支払いについて
10. 健康被害が発生した場合の対応・補償について
11. 個人情報の保護について
12. データの二次利用について
13. 試料・情報の取扱いについて
14. この臨床研究の結果の公表と返却について
15. この臨床研究の資金と利益相反について
16. 研究組織・連絡先

私は、本臨床研究について以上の項目を説明しました。

説明日：　令和　　年　　月　　日

説明者氏名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿（自署）

私はこの研究に参加するにあたり、研究の内容について担当者より十分な説明を受けました。研究の内容を理解しましたので、参加することについて同意します。

同意日：　令和　　年　　月　　日

氏名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿（自署）

Appendix B: Informed Consent Form for Patients in English

Request for participation in the research on geriatric assessment and communication support for treatment selection and continuation of treatment that meets the needs of elderly cancer patients

Official title of the research project: Randomized Controlled Trial to Develop a Program for Geriatric Assessment and Management by **M**obile **AP**p**L**ications for **E**lderly Patients with Advanced and Recurrent Cancer(**MAPLE**)

<Summary of this Explanatory Consent Document>

- This explanation document explains the content of the clinical research and has been prepared to supplement the researcher's explanation to help potential research subjects consider participation in the clinical research, understand the content of this research, and think about whether they want to participate or not. Please make sure to listen to the explanation from the researcher, and if you have any questions, please do not hesitate to ask the researcher.
- You can decide for yourself whether or not to participate in this clinical study. If you want more information, you can read the research protocol. You will not be disadvantaged in any way if you do not participate in this study.
- We plan this study because we believe that by appropriately assessing the physical and psychological functions and social life status of elderly patients, suggesting necessary support, and discussing aging-related treatment and life concerns with physicians, we can help patients make treatment choices that better meet their needs and continue treatment.
- The purpose of the study is to (1) assess the physical, mental, and lifestyle changes that occur with aging and provide regular support to lessen the impact on treatment, and (2) see if sharing treatment and recuperation concerns associated with aging between patients and their doctors will improve communication during office visits.
- Study participants must be diagnosed with cancer of the digestive organs (esophagus, stomach, colon, liver, bile, pancreas), be 70 years of age or older, and be planning to receive new chemotherapy or change medications.
- Under the new initiative, a questionnaire survey will be conducted on the patient's physical and psychological functions and social life situation, and based on the results, necessary support will be individually suggested. In addition, question support will be provided so that patients can discuss concerns associated with aging with their physicians.

1. About the clinical study and this information memorandum

Much research is needed to develop methods of diagnosis and treatment of diseases. Current methods of diagnosis and treatment have been researched and advanced over a long period of time.

The National Cancer Center is also actively involved in various types of research to contribute to the development of cancer treatment. Among these studies, those conducted with the cooperation of patients are called “clinical research”. Clinical research is only possible with your understanding and cooperation, and current treatments are the result of the cooperation of many people who have participated in research to date.

In conducting this clinical research, consideration for the human rights and safety of patients is reviewed and approved by the Institutional Review Board of the National Cancer Center to determine whether the research will contribute to the development of medical science, and permission is granted by the President. At that time, the research is also reviewed to ensure that it is planned in accordance with the ethical guidelines established by the government.

This explanation document explains the content of the clinical research and has been prepared to supplement the researcher's explanation to help potential research subjects consider participation in the clinical research, understand the content of this research, and think about whether they want to participate or not. Please make sure to listen to the explanation from the researcher, and if you have any questions, please do not hesitate to ask the researcher.

2. Freedom of participation

You can decide for yourself whether or not to participate in this clinical study.

If you would like to know more about this clinical research, you can read the research protocol to the extent that it does not interfere with the conduct of the research.

If you choose not to take part in the study, you are guaranteed to receive treatment as usual and you will not be disadvantaged. You can also withdraw from the study at any time and for any reason, even after you have agreed to participate in the study. You will not be disadvantaged in this way.

Please read the detailed explanation of this clinical research from now on, and if you understand the content of the clinical research and wish to participate after receiving an explanation from the researcher, please tell the person explaining the research that you agree to the research.

3. Who is eligible for this clinical study?

This study will include patients who have been diagnosed with advanced or recurrent stage gastrointestinal cancer (including esophageal, stomach, colorectal, liver, biliary tract, and pancreatic cancer), are 70 years of age or older, and are newly receiving chemotherapy or will be changing their chemotherapy medications.

If you participate in the study and do not have any problems in assessing your physical and mental function and social life status in the first questionnaire (geriatric assessment), you will not be eligible for subsequent questionnaires or interviews (only medical record surveys will be conducted after 3 and 6 months regarding chemotherapy-related adverse events).

4. The significance and purpose of this clinical study

In chemotherapy for patients over 70 years old, it is recommended to consult with the patient to determine the best treatment, taking into account the patient's age, physical and mental functions, and social life status, as well as the patient's values and preferences. Some elderly cancer patients may be anxious about communicating their intentions to their doctors. In this study, we will conduct interviews and support them to ask their doctors questions that are in line with their intentions.

In this study, we plan to conduct an application-based questionnaire (geriatric assessment) as a new consultation method to check the patients' physical and mental functions and social life status, and to provide support to reduce the impact of aging on treatment, as well as to investigate whether communication support using a pamphlet-based interview would improve the discussion between patients and doctors. The study was designed to determine whether communication support would improve patient-physician communication. This study may lead to safer and more effective treatment.

We will also examine the relationship between the initial questionnaire on physical and mental function and social life status (geriatric assessment) and adverse events of chemotherapy.

5. Methods of this clinical study

If you participate in the study, you will be asked to complete a questionnaire (geriatric assessment) about your physical and mental functions and social life situation. The questionnaire is completed using an application and takes approximately 10 to 20 minutes to complete. If no support is suggested in this questionnaire (geriatric assessment) for physical and mental function and social status, the patient will not be eligible for further interviews, questionnaires, or consultation recordings. We will only conduct a medical record survey at 3 and 6 months for chemotherapy adverse events.

Patients for whom some support is suggested in the initial questionnaire (geriatric assessment) will have their consultation recorded once in order to learn how they are doing during the consultation. In addition, medical records related to the treatment will be reviewed by the research investigators from the medical records. The information to be confirmed from the medical record includes the name of diagnosis, characteristics of the diagnosed cancer (Stage and histological type), details of treatment, degree of symptoms associated with the treatment, nursing insurance, and medical fee schedule. In addition, if you are transferred to a different hospital, we may inquire about this information with your doctor's permission to the hospital to which you are being transferred.

Some individuals (new consultation groups) will be interviewed by interventionists who have completed prior training based on the intervention manual. Interviews will be conducted during the waiting time of the consultation or between treatments, and will last 30-40 minutes the first time and 10-20 minutes the second and subsequent times. Only with your consent, we will record the interview. At that time, we will provide you with information about the relationship between your physical and mental conditions and treatment using a pamphlet that we have individually prepared based on the questionnaire you have filled out using the application. We will also suggest specific support that you can receive to reduce the impact of aging on your treatment, depending on your physical and emotional condition. This information will also be shared with your physician. In addition, the new consultation group will check in with you in person or by phone to see how you are doing in terms of support to reduce the impact of aging on your treatment.

The others (regular consultation group) will not be interviewed. Which group you will be in is decided by a computerized randomization method called "randomization", not by your own wishes or the doctor's decision. This method is considered the best and most scientific method because it allows

you to compare whether the method of support you want is really good or not by dividing you into groups with almost the same conditions (age, physical condition, disease status, etc.) other than the method of support you want to study. In both groups, you will discuss your treatment with your doctor, and you are free to decide at any time if you wish to use the outpatient consultation services of social workers, nurses, psychologists, etc. If you are admitted to the regular consultation group, you will also receive a brochure for your new consultation group, if you wish, after the end of the study period.

Specific schedule

The new group of patients will be interviewed twice, once at the study entry visit and once three months later at the follow-up visit. In addition, the new group will check in with you every month, either in person or by telephone, to see how you are doing and to check on the implementation of your care to reduce the impact of aging on your treatment. We may call you to arrange a time to meet with you. There will be no interviews in the regular consultation group. For both groups, questionnaires will be administered three times: at the study entry visit and at visits 3 and 6 months later. At the 12-month follow-up visit, the researcher will only examine your medical records.

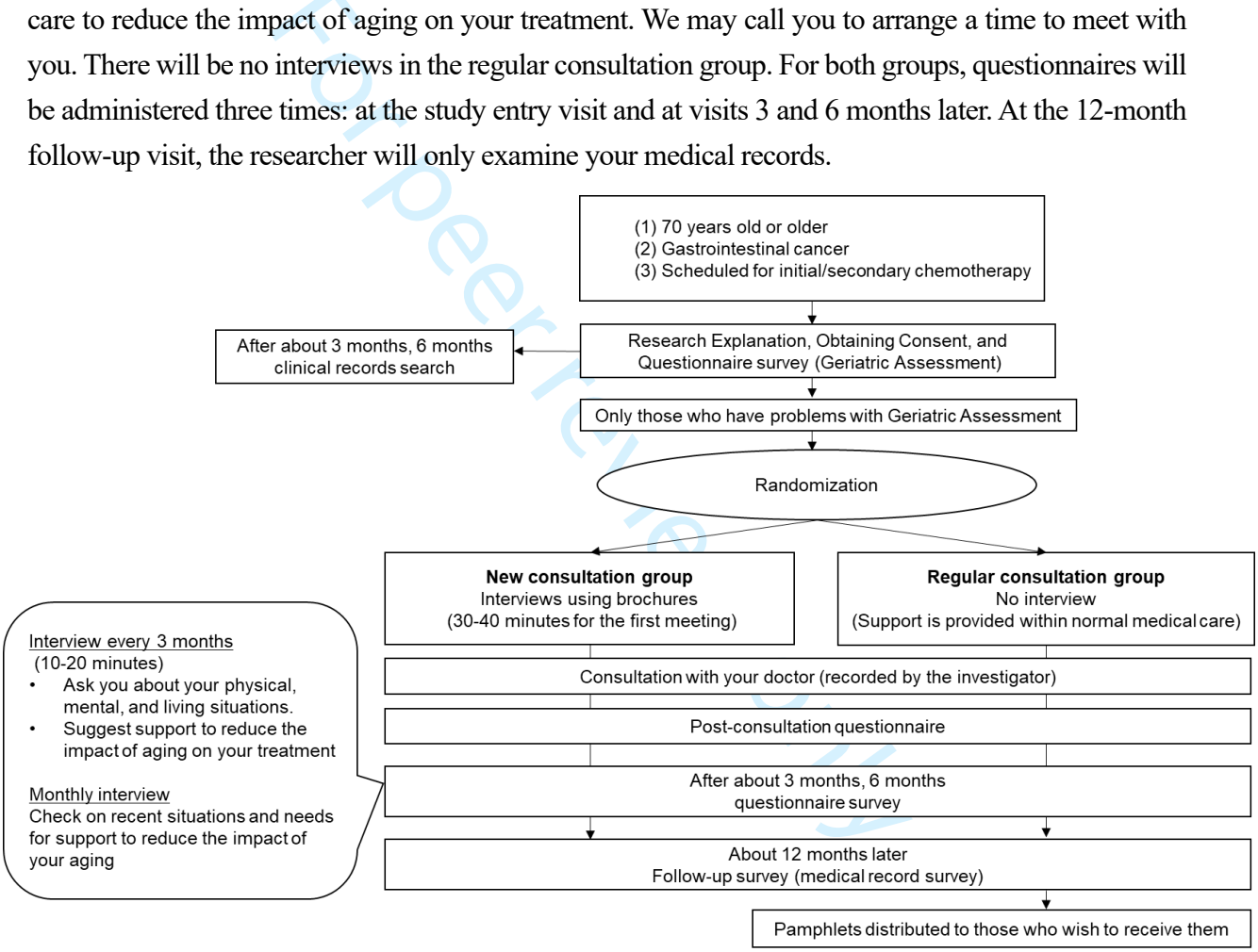

Figure 1. Overview of the study

6. Anticipated benefits and disadvantages of participation in the study

Patients who participate in the study may benefit from the new approach, including improved communication with their doctors, better understanding of their disease and treatment, and reduced anxiety in the long term. In addition, receiving support for their physical and emotional conditions may reduce the impact of aging on their treatment, allowing them to continue to receive safer and more effective treatment. However, one disadvantage of participating in the study is the potential time

commitment. The initial consultation with the new initiative will take 40 minutes to an hour to complete a questionnaire and meet with the patient, and the second and subsequent consultations will take 20 to 30 minutes. Maximum consideration will be given to waiting time in the outpatient clinic and to conducting the consultation when it is convenient for patients who are undergoing treatment.

We do not believe that patients with usual medical examination will benefit from participating in this study. However, they can contribute to the establishment of new support methods. On the other hand, it will take 10-20 minutes to answer the questionnaire.

If you experience any inconvenience or difficulty in participating in the research, please do not hesitate to inform the staff member in charge or the researcher.

7. Treatment and support if you do not participate in this clinical study

If you choose not to participate in this clinical study, you will still receive the treatment and support that we think is most appropriate for you. If you choose not to participate in the study, you will still be able to discuss your treatment with your doctor and, as with your regular consultations, you are always free to decide if you would like to use the outpatient consultation service, which includes a psychologist and social worker.

8. Planned duration of the entire clinical research

The study enrollment period for patients participating in this clinical study is planned to be three years from the date the study is approved, and the follow-up period for participating patients will be one year after enrollment ends.

The overall duration of the study will be five years from the date the study is approved.

9. Cost sharing and payment of honorarium

Other medical examinations and tests required as a result of your participation in this clinical research will be covered by health insurance, but you will be expected to pay your own costs as if you were receiving regular medical treatment. No rewards will be given for participation in the research.

10. Response and compensation in the event of a health hazard

This clinical study is supported by questionnaires and interviews and is not expected to cause any unanticipated serious side effects or other health problems.

11. Protection of personal information

If you participate in this clinical research, your personal information and some of the records related to your medical information will be stored within the Institute for Cancer Control, National Cancer Center Cancer, where the research office is located, and the Department of Supportive Care, National Cancer Central Hospital, where the data center is located, and the principal investigator will be responsible for managing them. Information collected for data management for use in clinical research

will include medical record number, date of birth, and other information (age, gender, cancer type, advanced stage, and treatment regimen). We may also obtain your name, address, and telephone number as personal information to mail you questionnaires or to contact you by telephone.

In all correspondence between the research office and the hospital, we will use the unique study number assigned to you in the study, rather than your name. This unique study number is very important to ensure that your information as a participant in the clinical study is properly managed during subsequent investigations, even if the doctor has been transferred.

We may provide information to researchers involved in the research who are in charge of data analysis with data that does not contain personal information under appropriate management. The information to be provided includes information on diagnosis and treatment and the results of questionnaires.

[Data analyst for this clinical study]

Keita Mori : Statistical Analysis Room Director, Clinical Trial Coordination Office, Shizuoka Cancer Center

We have obtained permission from the Institutional Review Board of the National Cancer Center regarding the method of protection and management of personal information in clinical trials. The Research Office and the collaborating institutions will make every effort to ensure that this information is not disclosed to outside parties or used for purposes other than those of the clinical study. If you are interested in participating in this clinical study, we ask that you consent to the use of your personal information.

In order to check from a third party's point of view whether this research is being carried out properly, people from the department in charge of auditing clinical research at our center and others may have access to your medical records and other medical records. In such cases, these parties are bound by confidentiality agreements and your personal information will be protected.

12. Secondary use of data

Information obtained from this clinical research may be used for secondary purposes. In such cases, the data will be anonymized so that no personally identifying information is linked, and will be used only for the purpose of helping to improve the quality of life of cancer patients.

13. Handling of samples and information

We will keep the information obtained from this clinical research study for 5 years from the date of submission of the study completion report or 3 years from the date of publication of any article related to this study, whichever is later, according to the rules of the institution to which the researcher is affiliated. This is currently considered a necessary step to ensure that the results of the research can be verified by someone else at a later date. If we need to dispose of the data after the specified period, we will process them in such a way that it is not immediately clear to whom they belong. All electronic media, including audio recordings, will be deleted completely and paper media will be shredded and destroyed.

14. Publication and return of the results of this clinical study

The results obtained from this clinical study will be published in medical societies and medical journals. Your name and other personally identifiable information will not be used in the publication.

Please note that the analysis results of this clinical study are at the research stage and, in principle, will not be shared with you. However, if they become more likely to be useful for your health condition, your doctor may contact you again after careful consultation with specialists and physicians. Information about this clinical trial will be registered and released to the University Hospital Medical Information Network Clinical Trials Registration System (UMIN-CTR) [https://www.umin.ac.jp/ctr/index-j.htm] in accordance with established regulations.

15. Funding and conflicts of interest for this clinical study

(1) Explanation of "conflict of interest"

Conflict of interest in clinical research refers to a situation in which a researcher receives financial benefits (e.g., rewards, research expenses, shares, etc.) from a company or other entity, and the existence of such benefits may affect the results of the clinical research.

(2) Statement regarding the existence or non-existence of conflicts of interest and explanation of the details

This study is funded by a Grant-in-Aid for Japan Agency for Medical Research and Development (Principal Investigator: Maiko Fujimori, Project ID: 21ck0106682h0001). This study do not receive any funding or free drugs from any specific organization, so there are no other potential conflicts of interest regarding the research organization as a whole.

(3) Description of how conflicts of interest are managed

Each participating institution manages conflicts of interest for researchers at its own institution. The Conflict of Interest Committee at the National Cancer Center manages conflicts of interest for researchers at our center. If you would like more information, please contact your physician.

16. Research organization / Contact

If you have any questions or concerns about this clinical study, or if you wish to withdraw your consent, please do not hesitate to ask us. Also, if you would like to know the results after the clinical research is finished, please contact the research office. The office is open weekdays from 9:00 to 17:00.

Principal Investigator: Maiko Fujimori
Research Office: Ayumu Matsuoka
Contact: Institute of Cancer Control, National Cancer Center
Address: 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045
TEL：03-3547-5201 (PHS 5539 / Ext. 3329)

E-mail: aymatsuo@ncc.go.jp (Ayumu Matsuoka)

Collaborative Research Person

Atsuo Takashima, Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital

Takuji Okusaka, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital

Keita Mori, Clinical Trial Coordination Office, Shizuoka Cancer Center

Fumio Nagashima, Department of Medical Oncology, Faculty of Medicine, Kyorin University

For your custody / For your medical record

Agreement

To: Director of National Cancer Center Hospital

Title of Project: Randomized Controlled Trial to Develop a Program for Geriatric Assessment and Management by Mobile Applications for Elderly Patients with Advanced and Recurrent Cancer(MAPLE)

1. About the clinical study and this information memorandum
2. Freedom of participation
3. Who is eligible for this clinical study?
4. The significance and purpose of this clinical study
5. Methods of this clinical study
6. Anticipated benefits and disadvantages of participation in the study
7. Treatment and support if you do not participate in this clinical study
8. Planned duration of the entire clinical research
9. Cost sharing and payment of honorarium
10. Response and compensation in the event of a health hazard
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13. Handling of samples and information
14. Publication and return of the results of this clinical study
15. Funding and conflicts of interest for this clinical study
16. Research organization / Contact

I have explained the above items about this clinical study.

Explanation Date:

Name of person providing explanation(Signature):

I have received a full explanation of the study from the person in charge of the study before participating in this study. I understand the content of the study and agree to participate.

Date of agreement:

Name (Signature):

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill8W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	7
Funding	#4	Sources and types of financial, material, and other support	37
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	36
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	37
Roles and responsibilities: sponsor and funder	#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	37
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	n/a

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	9-12
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9-12
Objectives	#7	Specific objectives or hypotheses	11-12
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, non-inferiority, exploratory)	12-13
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	12-13

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)	13-14
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-22
Interventions: modifications	#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)	22
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	22
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	22-28

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)	22-23, Figure 2
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	29
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13-14
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	17
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	17

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection plan	#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	22-28

Data collection plan: retention	#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	22-28
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	31
Statistics: outcomes	#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	30
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	30
Statistics: analysis population and missing data	#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)	30
Methods: Monitoring			
Data monitoring: formal committee	#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	31

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	30
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	28
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	31
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13, 39
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)	32

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	31
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	37-38
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
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	28-29
Dissemination policy: trial results	#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	32

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	31
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A
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	n/a