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Lifestyle and Empowerment Techniques in Survivorship of Gynecologic Oncology (LETSGO study).

A multicenter longitudinal cohort study using mobile health technology and biobanking.

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Introduction

The number of gynecological cancer survivors is increasing and there is a need for a more sustainable model of follow-up care. Today's follow-up model is time-consuming and patients have reported unmet needs regarding information about their cancer and strategies for managing the consequences of treatment. The main aim of this study is to assess health-related empowerment—in terms of patient education, psychosocial support, and promotion of physical activity—in a new follow-up model by comparing it to standard follow-up in a cohort study involving intervention hospitals and reference hospitals.

Methods and analysis

At the intervention hospitals, patients will be stratified by risk of recurrence and late effects to either 1 or 3 years' follow-up. Nurses will replace doctors in half of the follow-up visits and focus in particular on patient education, self-management, and physical activity. They will provide patients with information and guide them in goal setting and action planning. These measures will be reinforced by a smartphone application for monitoring symptoms and promoting physical activity. At the reference hospitals, patients will be included in the standard follow-up program. All patients will be asked to complete questionnaires at baseline and after 3, 6, 12, 24, and 36 months. Blood samples will be collected for biobanking at 3, 12, and 36 months. The primary outcome is health-related empowerment. Secondary outcomes include health-related quality of life, adherence to physical activity recommendations, time to recurrence, health care costs, and changes in biomarkers. Changes in these outcomes will be analyzed using generalized linear mixed models for repeated measures. Type of hospital (intervention or reference), time (measurement point), and possible confounders will be included as fixed factors.

Ethics and dissemination

The study is approved by the Regional Committee for Medical Research Ethics (2019/11093). Dissemination of findings will occur at the local, national, and international levels.

The protocol is registered on www.clinicaltrials.gov (NCT04122235).

Strengths and limitations of this study

- This is a large cohort study with a quasi-randomized design that reflects daily clinical practice.
- At intervention hospitals, nurses aim to empower the participants by providing information, helping with goal setting, and monitoring physical activity. These measures are reinforced with a smartphone application.
- The study has a translational approach with the establishment of a longitudinal biobank of samples of blood and blood components.
- A health economic evaluation will explore if the new follow-up program results in fewer scheduled appointments at the intervention hospitals, which may have an effect on resource utilization.
- With a non-randomized design, imbalances in prognostic factors between the groups cannot be entirely removed.

Introduction

The current global yearly incidence of gynecological cancer is almost 1.3 million cases and is expected to increase by 44.6% by 2040 (1). The increase in prevalence will pose challenges for post-treatment follow-up models, which are currently time-consuming, expensive, and lack evidence of efficacy regarding survival and quality of life (QoL) (2). Traditional hospital-based follow-up has been criticized for being too focused on the detection of recurrences and less attentive to physical and psychological rehabilitation after cancer treatment (3, 4). Consequently, survivors report unmet needs relating to their cancer treatment, comorbidities, and economic and family concerns (5). A small number of clinical and economic evaluations of alternative approaches to survivorship care after gynecological cancer have been reported (3). These include evaluations of nurse-led telephone follow-up and comparisons between more intensive and less intensive follow-up procedures (3, 6-8). One alternative model for delivering care in cancer survivorship is the risk-stratification model, whereby patients are stratified according to their risk of developing late effects of treatment or cancer recurrence (9). Only three randomized controlled trials (RCTs) comparing different follow-up models have been published to date, two in low-risk endometrial cancer patients (6, 7) and one in ovarian cancer patients (8). These studies are limited by small sample sizes (ranging from 112 to 156 participants) and short follow-up (ranging from 10 to 24 months) (6-8). A Cochrane review of follow-up after treatment for cervical cancer found no evidence from RCTs to support any specific follow-up model over others. Thus, well-designed prospective studies on follow-up models are needed (10).

Gynecological cancer survivors report a high prevalence of treatment-related symptoms that can affect their QoL. The most frequently reported symptoms are fatigue, neuropathy, lymphedema, sexual dysfunction, cognitive dysfunction, anxiety, and depression (11-16). Some of these symptoms may also be signs of disease recurrence (17). In a study of symptoms related to first recurrence after treatment for gynecological cancer, two-thirds of the patients experienced symptoms at recurrence, but only 55% sought care earlier than their scheduled visit (17), which may have delayed detection of recurrence and appropriate symptom management. This underlines the importance of providing education on alarm symptoms and motivating patients to actively manage their condition after gynecological cancer treatment (2, 18). In a cancer survivorship context, health-related empowerment refers to an individual's feelings of being able to manage the challenges of the cancer experience and of having a sense of control over their own life (19). The facilitation of empowerment through education and self-management strategies to enhance problem-solving skills, action planning and self-efficacy are components of the chronic care model developed by the MacColl Institute for Healthcare Innovation (2, 18, 20). To the best of our knowledge, only two studies have assessed follow-up models using a self-management approach after primary treatment for gynecological cancer (7, 21), one of which was a randomized controlled trial (7). In this trial, which focused on low-risk endometrial cancer patients, patient-initiated follow-up was compared to standard care 10 months after treatment (7). The women in the intervention group reported more fear of recurrence compared to women in the control group, which suggests that women may need organized support to feel reassured despite having a low risk of recurrence (7). In the other study, which included low-risk endometrial cancer patients, a majority of participants reported that patient-initiated follow-up enabled them to have more control over their own health. However, this study did not include a control group, so conclusions about effects compared to usual care could not be drawn (21).

A follow-up model designed to increase health-related empowerment provides opportunities for highlighting patients' lifestyle in terms of health behaviors, such as physical activity. It is well known that physical activity provides multiple psychological and physiological benefits after a cancer diagnosis and is associated with increased health-related QoL, as well as a reduced risk of cancer morbidity (22, 23). International health authorities recommend that all adults, including cancer survivors, should engage in moderate-intensity physical activity for a minimum of 150 min per week or vigorous-intensity physical activity for at least 75 min per week (24). Although patients often request information about health-promoting strategies, many gynecological cancer survivors find it difficult to alter their lifestyles without external motivation (25). Research has consistently shown that interventions targeting patient autonomy and self-regulation (the ability to act in one's own long-term best interest) can promote physical activity behavior changes (26). To date, only a small number of studies have examined the feasibility and effects of lifestyle interventions in gynecological cancer survivors. These studies have shown that lifestyle interventions have the potential to improve QoL and reduce fatigue (27).

Mobile health (mHealth) is a subset of the broader concept of electronic health and refers to the use of mobile devices to support the delivery of medical and public health care to individuals and populations. According to the World Health Organization, mHealth has the potential to transform health service delivery across the globe (28). In recent years, mobile web applications (apps) have increasingly been used to promote chronic disease management, including among patients with cancer (29-31). Regular reporting of a limited set of symptoms has been found to be an accurate and cost-effective way of detecting recurrences and treatment-related late effects in patients with cancer in the lungs and breasts (32, 33). Smartphone apps have also been used as tools to enhance physical function and physical activity in cancer patients (34, 35).

Studies indicate that pro-inflammatory cytokines are important in the pathophysiology of cancer symptoms, including psycho-behavioral symptoms (36) and that chronic inflammation increases the risk of cancer-related comorbidity and mortality (36-38). Furthermore, inflammation and metabolic status have been linked to metabolic syndrome, which is closely related to the incidence of endometrial cancer (39). Despite growing evidence of the role of biomarkers in cancer-related morbidity and QoL, studies investigating the contribution of biomarkers to gynecological cancer survivorship are limited.

Against this background, our research group has developed a follow-up program based on the principles of the risk-stratification model and the chronic care model involving a 1-year hospital follow-up for low-risk gynecological cancer patients or a 3-year follow-up for medium/high-risk patients. For half of the consultations, nurses will replace the doctors and will use evidence-based behavior change techniques to coach the cancer patients on how to take a more active role in managing their health conditions (40-42). The nurses will focus on information on symptoms of recurrence, management of late effects, goal setting for physical activity, action planning, review of goal setting, and monitoring of physical activity. The techniques will be reinforced with the multifunctional Lifestyle and Self-Management Techniques in Survivorship of Gynecologic Oncology (LETSGO) app, which includes the following functions (Figure 1):

1) Monitoring and self-reporting of symptoms (related to suspected recurrence or late effects)

2) Targeted information on treatment, signs of recurrence, and late effects of each gynecological cancer type
3) Promoting early rehabilitation by provision of information on physical activity, goal setting, and electronic reminders
The LETSGO follow-up model has been pilot-tested in 12 gynecological cancer patients (NCT03453788).

The aim of the LETSGO study is to evaluate a new program for follow-up after gynecological cancer. The program is based on risk stratification and patient self-management and includes nurse-led coaching, mHealth technology, and promotion of physical activity. It will be compared to the standard follow-up program, which follows Norwegian guidelines.
The objectives are to
(1) compare patient empowerment (primary outcome) in patients attending intervention hospitals and those attending reference hospitals at 12 months,
(2) compare health-related QoL between the intervention group and the reference group,
(3) compare physical activity between the intervention group and the reference group,
(4) compare time to detection of recurrence between the intervention group and the reference group,
(5) assess whether the intervention is cost-effective compared to current practice, and
(6) identify relationships between self-management, physical activity, and various biomarkers.

Methods

The study follows the SPIRIT (Standard Protocol Items: Recommendations for clinical trials) checklist (43) and World Health Organization Trial Registration Data Set.

Table 1 approximately here

Design

The LETSGO study is a longitudinal, quasi-experimental multicenter cohort study comparing a new follow-up program at intervention hospitals with the standard follow-up program at reference hospitals.

Study population

We have begun to recruit a cohort of women who have completed treatment for gynecological cancer. The study is being conducted at 10 Norwegian hospitals (five intervention and five reference hospitals). University hospitals, regional hospitals and all Norwegian health regions are equally distributed in both groups, and their standard follow-up routines do not differ (44). Participating hospitals are listed at www.clinicaltrials.gov. Medical specialists and study nurses will inform eligible patients about the study before the first follow-up visit after primary treatment has been completed.

Inclusion criteria

Eligible participants (1) have histologically verified cervical cancer (restricted to squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), endometrial cancer, ovarian cancer (restricted to epithelial type), or vulvar cancer; (2) have completed primary standard treatment and are scheduled for follow-up; (3) are able (both physically and cognitively) to complete patient-

reported outcome measures independently in Norwegian; (4) are ≥ 18 years; and (5) are able to provide informed consent.

Exclusion criteria
Patients are ineligible if they (1) are participating in a clinical treatment trial; (2) are on intravenous maintenance treatment (e.g., bevacizumab); (3) are cervical cancer patients who have been treated with trachelectomy.

Study timeline
Enrollment of participants started in November 2019 and is due to close in December 2024 or after accrual and the last patient visit is completed

Intervention hospitals

Nurse-led consultations
The low-risk group will be followed up for 1 year and the medium/high-risk group for 3 years (Table 1). Before entering the follow-up program, the participants will be assigned to either the low-risk group or the medium/high-risk group according to predefined risk criteria. The low-risk group includes patients with (1) cervical cancer FIGO (International Federation of Gynecology and Obstetrics) stage IA1 with negative cytology and human papilloma virus status at 9 months after treatment; (2) endometrial cancer FIGO stage IA or B with endometrioid adenocarcinoma grade 1 and no adjuvant therapy; or (3) ovarian cancer FIGO stage IA and no adjuvant therapy. The medium/high-risk group includes patients with (1) cervical cancer FIGO stage IA1 with positive cytology and human papilloma virus status at 9 months after treatment or any other FIGO stage; (2) endometrial cancer at any stage except FIGO stage IA/B with endometrioid adenocarcinoma grade 1; (3) ovarian cancer FIGO stage IA with adjuvant chemotherapy or FIGO stage IB to IVB; or (4) vulvar cancer at any stage.

The first visit will take place 3-5 weeks after treatment ends. A second nurse-led visit will take place 7-8 weeks after treatment. Thereafter, patients will alternate between nurse- and doctor-led consultations, as depicted in Figure 1. At the 3- to 5-week visit, the nurse will assess the women's physical and emotional status, as well as aspects of her lifestyle and family environment. Patients with smartphones or tablets will be introduced to the LETSGO app (see below), and patients without smartphones or tablets will be provided with an information booklet containing identical information to that contained in the app. At the second nurse-led visit, the nurse will explore the patient's previous physical activity and their motivation for future physical activity, using an autonomous supportive communication style inspired by motivational interviewing (45). In addition, the nurse will work with the patient to set individualized goals for physical activity in line with the patients' motivation and barriers. To encourage physical activity, the patients will receive a Garmin activity tracker and will be instructed to wear it all day through the entire study period. The step count is displayed in the LETSGO app when the patient's mobile phone is connected to the activity tracker. Goals will be reviewed and adapted accordingly at subsequent nurse-led visits.

The patients at the intervention hospitals will have access to the LETSGO app throughout the 3-year study period, irrespective of their risk group (except cervical cancer patients in the low-risk group

who have been treated with conization only, to avoid unnecessary fear of cancer recurrence in this low-risk population). At the final follow-up visit (at 12 months or 36 months, depending on the risk group), the nurse will emphasize the importance of being attentive to symptoms as signs of recurrence and of a healthy lifestyle for well-being. The patients will receive written information on whom to contact if they experience treatment-related side effects or suspect disease recurrence. A summary of the patient's treatment, potential side effects, and symptoms of potential recurrence will be sent to the patient's responsible general practitioner. The nurses involved in the study are familiar with gynecological cancer patients. They have participated in a 2-day intensive course covering relevant subjects, including gynecological cancer treatment, physical and mental treatment-related symptoms, symptoms of recurrence, benefits of physical activity, autonomous supportive communication style, and motivation and individualized goal setting for physical activity. The nurses' education was reinforced by an electronic learning program with modules covering these subjects, which they were required to complete before the course.

The LETSGO app

The app is available for smartphones and tablets. It contains information on the different gynecological cancers, as well as lifestyle information and advice. It is distributed through Apple Store and Google Play, and a personal code is required to open the study version.
The app consists of the following modules (Figure 1):

1. Disease-specific information (written and audiovisual) on ovarian, uterine, cervical, or vulvar cancer, signs of recurrence, and late effects after treatment
2. General lifestyle information
3. Physical activity exercises and programs with instructions (written and audiovisual) for both beginners and experienced persons
4. Physical activity goal setting: Participants will be asked to define a goal for the week (e.g., a 30-minute walk twice a week or strength exercise in a health studio three times a week).
5. Monitoring of symptoms of recurrence: Once monthly, the participants will be asked to rate 10 symptoms that may indicate recurrence.

Patient-reported outcome studies have shown that the most frequent symptoms of recurrence are pain and fatigue for all gynecological cancers and bleeding for endometrial and cervical cancer (17). To cover these symptoms, we have selected relevant items from the European Organisation of Research and Treatment of Cancer (EORTC) item library (46), adjusted to each cancer type. The 10 EORTC items in the app refer to the preceding week. For instance, patients treated for endometrial or cervical cancer will be asked, "Have you had abnormal bleeding from your vagina?". Each participant will rate the severity of their symptoms in the preceding week from 0 (not at all) to 3 (very much). If a predefined threshold is reached, the participant will receive an alert on their phone or tablet informing her that the answer given may indicate recurrence and advising her to phone the pre-saved telephone number of the gynecological outpatient clinic. We anticipate that some participants may refrain from making contact. Therefore, the database will be checked for flags at regular time points by the project data manager. Patient visits and imaging will be brought forward if recurrence is suspected.

Control hospitals

Patients will receive standard follow-up according to current guidelines. Standard follow-up in Norway consists of clinical examination with vaginal ultrasound three to four times a year during the first 2 years, twice a year for the next 3 years, and annually thereafter, depending on the recommendations of the patient's doctor.

Data collection

Data will be collected using medical records, patient registries, validated questionnaires (electronic or written), and blood samples. Primary and secondary outcomes will be measured for all participants at enrollment (for baseline data) and again at 3, 6, 12, 24, and 36 months. Biobank samples will be collected at 3, 12, and 36 months and at time of recurrence, if applicable). At each time point, a reminder will be sent within 3 weeks to any participant who does not return the questionnaire. For the intervention group, data will also be abstracted from the app and the activity tracker.

Primary outcome

Patient empowerment

The Health Education Impact Questionnaire (heiQ), a well-validated, widely used measurement system for comprehensively assessing the effects of health education programs on self-management, was selected to measure aspects of empowerment in a cancer setting (19, 47). It consists of 40 questions grouped into eight domains. Responses are given on four-point Likert scales ranging from "strongly agree" to "strongly disagree," and the ratings are summed for each domain: positive and active engagement in life; health-directed activity; skill and technique acquisition; constructive attitudes and approaches; self-monitoring and insight; health service navigation; social integration and support; and emotional well-being. Reverse scoring is applied to emotional items, with higher scores indicating higher levels of empowerment. The heiQ has been translated into several languages and has been validated in a Norwegian population (48).

Secondary outcomes

Health-related QoL

Health-related QoL will be measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (49) and the EuroQol 5 Dimensions Questionnaire (EQ-5D) (50). Regarding the EORTC QLQ-C30, the scores of the five functional scales and one global QoL scale are converted to a 0–100 scale (49). A higher score reflects a better level of functioning and better QoL. Tumor-specific complaints are measured using the disease-specific supplements EORTC QLQ-EN24 (51) for endometrial cancer, EORTC QLQ-OV28 (52) for ovarian cancer, EORTC QLQ-CX24 (53) for cervical cancer, and EORTC VU-34 (under development, phase 4) for vulvar cancer. The EORTC instruments (except EORTC VU-34) have been used in studies of gynecological cancer survivors, some of which were conducted in Norway (15, 16, 54). The disease-specific instruments measure symptoms related to the respective tumor types (urological, intestinal, sexual, and vaginal symptoms). The EQ-5D consists of two principal measurement components. The first is a descriptive system, which defines health-related QoL in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), while the second is a visual analog scale (50).

Physical activity

Self-reported physical activity will be assessed using the short form of the International Physical Activity Questionnaire (IPAQ-sf) according to the guidelines for data processing and analysis developed by the IPAQ group (55). Exercise stage/readiness to change will be assessed using one item: "Please indicate which alternative corresponds with your current physical activity level or your interest in physical activity." Responses are given on a five-point ordinal scale from the exercise stages of change assessment instrument (56), which is based on the trans-theoretical (stages of change) model (57). The scale represents five different stages of change, ranging from 1 = "Not physically active and I do not intend to become more physically active during the next 6 months" (pre-contemplation stage) to 5 = "Physically active and I have been so for more than 6 months" (maintenance stage). Step count data imported from the Garmin activity tracker into the LETSGO app will be compared with self-reports of physical activity.

Fear of cancer recurrence

The Health Worries subscale of the Impact of Cancer (IOC) scale will be used to assess fear of cancer recurrence (58). The module consists of six questions, including questions on worry about the future, worry about health due to cancer, and worry about recurrence. Items are scored on a five-point intensity scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores reflect greater fear of cancer. The IOC has been validated in oncology patients in oncology settings (58).

Health care utilization

Health care utilization will be assessed by asking patients about the frequency of their contact with their gynecologist and primary care physician and about how many health care visits were related to cancer. We will also assess how often the patients use additional care services (e.g., psychologist, rehabilitation course, physical therapist).

Health economic evaluation

The EQ-5D is the generic measure preferred by the UK National Institute of Health and Care Excellence for cost-effectiveness and comparative purposes, which in turn has affected guidelines in several other countries, including Norway (50). Quality-adjusted life years (QALYs) will be calculated based on the area-under-the curve principle, taking into account both health-related QoL and survival of the patients during the 3-year follow-up period. Health care utilization at participating hospitals during the trial will be gathered for both groups. Health care utilization in other parts of the health care sector will be gathered from the following registry data sources: the Norwegian Prescription Database (www.reseptregisteret.no), which contains data on all medical prescriptions redeemed from Norwegian pharmacies; the Norwegian Patient Registry, which includes data on diagnostic information (ICD-10), medical treatment, length of hospital stay, and discharge data; the Municipal Patient and User Register (KPR); the individual-based care and care statistics registry (https://helsedirektoratet.no/iplos-registeret) for variables related to use of specialist and primary health care services; the Control and Payment of Health Reimbursement Database (https://helfo.no/) regarding GP visits, physiotherapy and health transportation; and the social security event database (FD-trygd). The costs of the intervention will be considered along with differences in resource use during follow-up and differences in QALYs to assess the incremental cost-effectiveness of the intervention compared to the control.

Biobanking

Blood samples will be collected at defined time points, as described in Table 1. Standard operating procedures (SOP) have been established for blood and sera collections. The blood samples will be processed in components and stored at −80°C. Three 6 ml EDTA samples will be collected and immediately centrifuged. From these, buffy coat (for isolation of genomic DNA) and plasma (for purification of circulating tumor DNA) will be isolated and stored in cryo tubes. Three SST II 5 ml serum Vacutainers will be collected and centrifuged after 30 min of coagulation time. Serum (for cytokine and metabolite analysis) will then be transferred to cryo tubes for storage. The consented SOP has been introduced at the participating hospitals, with an alternative protocol for the smaller hospitals without microcentrifuges.

Other measurements

Comorbidity will be assessed using the Self-Administered Comorbidity Questionnaire (SCQ) (59), which consists of 16 common and three optional medical conditions. Patients will be asked to indicate whether they have the condition, if they are receiving treatment for it, and if it limits their activities. For the present study, we will only ask whether the patients have any of the common conditions. The SCQ has well-established validity and reliability in Norwegian patients with chronic medical conditions (59, 60). Demographic information such as age, education, marital status, and treatment will be obtained from baseline questionnaires and medical records.

Sample size calculation

Sample size calculations were based on the primary outcome of interest. From a review of the available literature (48, 61), we anticipated that the change in mean value of the heiQ domain (self-monitoring and insight) from baseline to 12 months would be higher in the intervention group (62). A 10% difference is considered clinically relevant (63). Assuming a common standard deviation of 1.4 and using the customary significance level alpha of 5% and power of 80%, we determined that 343 individuals in each group would be needed to reveal a clinically relevant difference of 10% or more. Accounting for a dropout rate of 10%, we determined that 377 would be needed in each group.

Statistical analyses

Data will be analyzed after 1 and 3 years of follow-up. Data will be presented as counts and percentages (categorical variables) and mean and standard deviation or median and range for continuous data following normal or skewed distribution, respectively. Pairs of categorical variables will be compared using a chi-square test or, for small numbers, Fisher's exact test. Univariate analysis for comparison of continuous variables will be performed using a t-test for normally distributed data or the Mann-Whitney Wilcoxon test for variables with skewed distribution. Changes in the main outcome will be analyzed using generalized linear mixed models (GLMM) for repeated measures, as the outcomes are all continuous. As all included individuals will be assessed at several time points (baseline, 3, 6, 12, 24, and 36 months), statistical dependencies will exist. We will adjust for these using an unstructured covariance matrix if the model converges; if the model does not converge, we will fit a more specified covariance matrix. Type of hospital (intervention or reference), time (measurement point), and possible confounders identified when comparing patients at the intervention and control hospitals will be included as fixed factors. To account for added variation caused by enrolling participants at 10 different hospitals, we will include each hospital as a random factor. As GLMM models use all available observations, no imputation of missing data will be necessary. The results will be expressed as estimated means with 95% confidence intervals for each

time point and type of hospital (intervention vs. control). Differences in means between the intervention and control groups for each assessment point will be estimated. Time to recurrence will be modeled using survival analysis methodologies. Specifically, we will use Kaplan-Meier curves to depict crude time to recurrence and a Cox model to estimate hazard ratios for recurrence. The economic analyses will include controlling for enrollment differences and sensitivity analyses, according to international guidelines (63).

Patient involvement

We appointed a user panel of three women who had been treated for gynecological cancer and had no former experience with mHealth. The users have participated in several meetings since the initial planning of the study, and the resulting follow-up model has been adjusted based on their feedback and opinions. The users have read and commented on the protocol and have been involved in the development of the app. They have given their opinions on both the content of the app and the nurse-led consultations.

Ethics and dissemination

The LETSGO study has been approved by the Regional Committee for Medical and Health Research Ethics of South East Norway (2019/11093). The protocol is registered at www.clinicaltrials.gov (NCT04122235). The institutional review board and the data protection officer at each of the study sites have also approved the study. All patients will receive oral and written information about the study, and written informed consent will be collected prior to enrollment. An electronic case report form is used, and participants receive a unique subject number and subject identifier. Data are entered under this identification number onto a central database stored on secured servers. The servers are protected by firewalls and are patched and maintained according to best practice. The study investigators retain the right to access data. It is estimated that the study will be completed in 2024, after which the data analysis and the results will be disseminated.

Authors' contributions: IV, SB and ID conceived the study in collaboration with the other authors. IV was responsible for writing the protocol. M Skorstad, M Småstuen, KL, TW and LPF provided critical feedback during the conception of the study and the writing up of the protocol.

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Table1. Overview of all outcome measures and assessment times of the LETSGO study

Outcomes	Measurement instrument	Intervention hospitals											Reference hospitals								
		B[1]	3w[2]	6w	3m[3]	6m	9m	12 m	15 m	18 m	21 / 30 m	24 / 36 m	B	3m[4]	6m	9m	12 m	15 m	18 m	21/ 30 m	24/ 36 m
Questionnaires																					
Psychosocial outcomes																					
Patient empowerment	heiQ[6]	X			X	X		X				X	X	X	X		X				X
Generic QOL[5]	EQ-5D[7]	X			X	X		X				X	X	X	X		X				X
Disease specific QOL	EORTC QLQ-C30[8]	X			X	X		X				X	X	X	X		X				X
Tumor specific QOL	EORTC QLQ modules[9] CX24,	X			X	X		X				X	X	X	X		X				X
	EN24, OV28 and VU34	X			X	X		X				X	X	X	X		X				X
Cancer worry	IOC[10] worry subscale	X			X	X		X				X	X	X	X		X				X
Sexuality	SQOL-f[11] selected items	X			X	X		X				X	X	X	X		X				X
Follow-up care	Study-specific questions	X			X	X		X				X	X	X	X		X				X
Personal factors																					
Demographic variables	Standard questions	X			X	X		X				X	X	X	X		X				X
Comorbidity	SCQ[12]	X			X	X		X				X	X	X	X		X				X
Lifestyle factors	IPAQ-SF[13], ESAI[14]																				
Physical activity	Standard questions	X			X	X		X				X	X	X	X		X				X
Alcohol use	Standard questions	X			X	X		X				X	X	X	X		X				X
Smoking		X			X	X		X				X	X	X	X		X				X
Clinical factors	eCRF[15]																				
Medical history	eCRF	X											X								
Medication	Blood pressure, pulse,	X											X								
Vital signs	weight	X		X		X		X		X		X									
Performance status	ECOG[16] status	X		X		X		X		X		X									
Gynecological examination	NA[17]				X		X		X		X			X	X	X	X	X	X	X	X
LETSGO intervention (nurse)																					
Introduction to LETSGO-app	NA			X		X		X		X		X									
Assessment of rehabilitation needs	NA			X		X		X		X		X									

Set goals for physical activity	NA			X																
Follow up goals for physical activity	NA					X		X		X		X								
Motivating interview	NA	X		X		X		X		X		X								
Assessment of late-effects	Study-specific chart					X		X		X		X								
Visits at out-patient clinic	NA																			
Low risk group intervention		X	X		X		X													
Medium/high risk group intervention		X	X		X		X		X		X									
Reference group (all)													X	X	X	X	X	X	X	X
Biological factors																				
General laboratory	Blood	X			X	X		X				X	X	X	X		X			X
Biomarkers	Blood				X			X				X[18]	X	X			X			X[18]

[1]Baseline; [2]Weeks; [3]Months; [4]At reference hospitals, first questionnaire/blood tests may be collected at 3 months; [5]Quality of Life; [6]Health Education Impact Questionnaire; [7]EuroQol 5 dimensions questionnaire; [8]The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; [9]Modules: cervix, endometrium, ovarian, vulvar; [10]The Impact of Cancer Questionnaire; [11]Sexual Quality of Life–Female Questionnaire; [12]Self-Administered Comorbidity Questionnaire; [13]Physical Activity Questionnaire Short-Form [14]Exercise Stage Assessment Instrument; [15]Electronic Case Report Form; [16]Eastern Oncology Cooperative Group; [17]Not applicable; [18]Biomarkers at 3, 12 and 36 months.

Figure 1. The LETSGO-app (©A.Gjoerv) or Figure 1. The LETSGO-app (Created by A. Gjoerv)

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Lifestyle and Empowerment Techniques in Survivorship of Gynecologic Oncology (LETSGO study).

A study protocol for a multicenter longitudinal intervention study using mobile health technology and biobanking.

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Introduction
The number of gynecological cancer survivors is increasing and there is a need for a more sustainable model of follow-up care. Today's follow-up model is time-consuming and patients have reported unmet needs regarding information about their cancer and strategies for managing the consequences of treatment. The main aim of this study is to assess health-related empowerment—in terms of patient education, psychosocial support, and promotion of physical activity—in a new follow-up model by comparing it to standard follow-up in a quasi-randomized study involving intervention hospitals and control hospitals.

Methods and analysis
At the intervention hospitals, patients will be stratified by risk of recurrence and late effects to either 1 or 3 years' follow-up. Nurses will replace doctors in half of the follow-up visits and focus in particular on patient education, self-management, and physical activity. They will provide patients with information and guide them in goal setting and action planning. These measures will be reinforced by a smartphone application for monitoring symptoms and promoting physical activity. At the control hospitals, patients will be included in the standard follow-up program. All patients will be asked to complete questionnaires at baseline and after 3, 6, 12, 24, and 36 months. Blood samples will be collected for biobanking at 3, 12, and 36 months. The primary outcome is health-related empowerment. Secondary outcomes include health-related quality of life, adherence to physical activity recommendations, time to recurrence, health care costs, and changes in biomarkers. Changes in these outcomes will be analyzed using generalized linear mixed models for repeated measures. Type of hospital (intervention or reference), time (measurement point), and possible confounders will be included as fixed factors.

Ethics and dissemination
The study is approved by the Regional Committee for Medical Research Ethics (2019/11093). Dissemination of findings will occur at the local, national, and international levels.

Trial registration number NCT04122235

Strengths and limitations of this study

- LETSGO is the first multisite, comprehensive clinical study to investigate nurse-led patient education reinforced with a smartphone application compared to traditional follow-up after gynecological cancer assessed with validated questionnaires.
- The longitudinal quasi-randomized design reflects daily clinical practice and allows us to estimate possible changes over time defining the temporal sequence of changes and providing stronger evidence for causality.
- The study has a translational approach with the establishment of a longitudinal biobank of samples of blood and blood components.
- A health economic evaluation will explore if the new follow-up program results in fewer scheduled appointments at the intervention hospitals, which may have an effect on resource utilization.
- The primary limitation of this study is the quasi-randomized design which may lead to imbalances in prognostic factors between the groups.

Introduction

The current global yearly incidence of gynecological cancer is almost 1.3 million cases and is expected to increase by 44.6% by 2040[1]. The increase in prevalence will pose challenges for post-treatment follow-up models, which are currently time-consuming, expensive, and lack evidence of efficacy regarding survival and quality of life (QoL)[2]. Traditional hospital-based follow-up has been criticized for being too focused on the detection of recurrences and less attentive to physical and psychological rehabilitation after cancer treatment[3, 4]. Consequently, survivors report unmet needs relating to their cancer treatment, comorbidities, and economic and family concerns[5]. A small number of clinical and economic evaluations of alternative approaches to survivorship care after gynecological cancer have been reported to date[3], including three small randomized controlled trials (RCTs)[6-8]. Theses RTCs evaluate nurse-led telephone follow-up and comparisons between more intensive and less intensive follow-up procedures[3, 6-8]. Another alternative model for delivering care in cancer survivorship is the risk-stratification model, whereby patients are stratified according to their risk of developing late effects of treatment or cancer recurrence[9].

Gynecological cancer survivors report a high prevalence of treatment-related symptoms that can affect their QoL. The most frequently reported symptoms are fatigue, neuropathy, lymphedema, sexual dysfunction, cognitive dysfunction, anxiety, and depression[10-17]. Some of these symptoms may also be signs of disease recurrence[18]. Despite having symptoms at recurrence, it is shown that many patients fail to make an appointment earlier than scheduled [18]. This underlines the importance of providing education on alarm symptoms and motivating patients to actively manage their condition after gynecological cancer treatment[2, 19]. In a cancer survivorship context, health-related empowerment refers to an individual's feelings of being able to manage the challenges of the cancer experience and of having a sense of control over their own life[20]. The facilitation of empowerment through education and self-management strategies to enhance problem-solving skills, action planning and self-efficacy are components of the chronic care model developed by the MacColl Institute for Healthcare Innovation[2, 19, 21].

A follow-up model designed to increase health-related empowerment provides opportunities for highlighting patients' lifestyle in terms of health behaviors, such as physical activity. It is well known that physical activity provides multiple psychological and physiological benefits after a cancer diagnosis and is associated with increased health-related QoL, as well as a reduced risk of cancer morbidity[22, 23]. International health authorities recommend that all adults, including cancer survivors, should engage in moderate-intensity physical activity for a minimum of 150 min per week or vigorous-intensity physical activity for at least 75 min per week[24]. Although patients often request information about health-promoting strategies, many gynecological cancer survivors find it difficult to alter their lifestyles without external motivation[25]. In this context, research has consistently shown that interventions targeting patient autonomy and self-regulation (the ability to act in one's own long-term best interest) can promote physical activity behavior changes[26].

Mobile health (mHealth) is a subset of the broader concept of electronic health and refers to the use of mobile devices to support the delivery of medical and public health care to individuals and populations. In recent years, mobile web applications (apps) have increasingly been used to promote chronic disease management, including patients with cancer[27-29]. Regular reporting of a limited

set of symptoms has been found to be an accurate and cost-effective way of detecting recurrences and treatment-related late effects in patients with cancer in the lungs and breasts[30, 31]. Smartphone apps have also been used as tools to enhance physical function and physical activity in cancer patients[32, 33].

Studies indicate that pro-inflammatory cytokines are important in the pathophysiology of cancer symptoms, including psycho-behavioral symptoms[34] and that chronic inflammation increases the risk of cancer-related comorbidity and mortality[34-36]. Furthermore, inflammation and metabolic status have been linked to metabolic syndrome, which is closely related to the incidence of endometrial cancer[37]. Despite growing evidence of the role of biomarkers in cancer-related morbidity and QoL, studies investigating the contribution of biomarkers to gynecological cancer survivorship are limited.

The aim of the LETSGO study is to evaluate a new program for follow-up after gynecological cancer. The program is based on risk stratification and patient self-management and includes nurse-led coaching, mHealth technology, and promotion of physical activity. It will be compared to the standard follow-up program, which follows Norwegian guidelines.
The objectives are to
(1) compare patient empowerment (primary outcome) in patients attending intervention hospitals and those attending control hospitals at 12 months,
(2) compare health-related QoL between the intervention group and the control group,
(3) compare physical activity between the intervention group and the control group,
(4) compare time to detection of recurrence between the intervention group and the control group,
(5) assess whether the intervention is cost-effective compared to current practice, and
(6) identify relationships between self-management, physical activity, and various biomarkers.

Methods

The study follows the SPIRIT (Standard Protocol Items: Recommendations for clinical trials) checklist (Supplementary file 1)[38] and World Health Organization Trial Registration Data Set (Supplementary file 2).

Table 1 approximately here

Design

The LETSGO study is a longitudinal, quasi-experimental multicenter clinical study comparing a new follow-up program at intervention hospitals with the standard follow-up program at control hospitals.

The LETSGO follow-up model

Our research group has developed a follow-up program based on the principles of the risk-stratification model and the chronic care model comprising a 1-year hospital follow-up for low-risk gynecological cancer patients or a 3-year follow-up for medium/high-risk patients. For half of the consultations, nurses will replace the doctors and will use evidence-based behavior change techniques to coach the cancer patients on how to take a more active role in managing their health conditions[39-41]. The nurses will focus on information on symptoms of recurrence, management of late effects, goal setting for physical activity, action planning, review of goal setting, and monitoring

of physical activity. The techniques will be reinforced with the multifunctional Lifestyle and Self-Management Techniques in Survivorship of Gynecologic Oncology (LETSGO) app with several modules (Figure 1). The LETSGO follow-up model has been pilot-tested in 12 gynecological cancer patients (NCT03453788).

Study population

We have begun to recruit a cohort of women who have completed treatment for gynecological cancer. The study is being conducted at 10 Norwegian hospitals (five intervention and five reference hospitals). University hospitals, regional hospitals and all Norwegian health regions are equally distributed in both groups, and their standard follow-up routines do not differ[42]. Participating hospitals are listed at www.clinicaltrials.gov. Medical specialists and study nurses will inform eligible patients about the study before the first follow-up visit after primary treatment has been completed.

Inclusion criteria

Eligible participants (1) have histologically verified cervical cancer (restricted to squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), endometrial cancer, ovarian cancer (restricted to epithelial type), or vulvar cancer; (2) have completed primary standard treatment and are scheduled for follow-up; (3) are able (both physically and cognitively) to complete patient-reported outcome measures independently in Norwegian; (4) are ≥ 18 years; and (5) are able to provide informed consent.

Exclusion criteria

Patients are ineligible if they (1) are participating in a clinical treatment trial; (2) are on intravenous maintenance treatment (e.g., bevacizumab); (3) are cervical cancer patients who have been treated with trachelectomy.

Study timeline

Enrollment of participants started in November 2019 and is due to close in December 2024 or after accrual and the last patient visit is completed

Intervention hospitals

Nurse-led consultations

The low-risk group will be followed up for 1 year and the medium/high-risk group for 3 years (Table 1). Before entering the follow-up program, the participants will be assigned to either the low-risk group or the medium/high-risk group according to predefined risk criteria. The low-risk group includes patients with (1) cervical cancer FIGO (International Federation of Gynecology and Obstetrics) stage IA1 with negative cytology and human papilloma virus status at 9 months after treatment; (2) endometrial cancer FIGO stage IA or B with endometrioid adenocarcinoma grade 1 and no adjuvant therapy; or (3) ovarian cancer FIGO stage IA and no adjuvant therapy. The medium/high-risk group includes patients with (1) cervical cancer FIGO stage IA1 with positive cytology and human papilloma virus status at 9 months after treatment or any other FIGO stage; (2) endometrial cancer at any stage except FIGO stage IA/B with endometrioid adenocarcinoma grade 1; (3) ovarian cancer FIGO stage IA with adjuvant chemotherapy or FIGO stage IB to IVB; or (4) vulvar cancer at any stage.

The first visit will take place 3-5 weeks after treatment ends (chemotherapy, radiotherapy or surgery completion). A second nurse-led visit will take place 7-8 weeks after treatment. Thereafter, patients will alternate between nurse- and doctor-led consultations, as depicted in Figure 1. At the 3- to 5-week visit, the nurse will assess the women's physical and emotional status, as well as aspects of her lifestyle and family environment. Patients with smartphones or tablets will be introduced to the LETSGO app (see below), and patients without smartphones or tablets will be provided with an information booklet containing identical information to that contained in the app. At the second nurse-led visit, the nurse will explore the patient's previous physical activity and their motivation for future physical activity, using an autonomous supportive communication style inspired by motivational interviewing [43]. In addition, the nurse will work with the patient to set individualized goals for physical activity in line with the patients' motivation and barriers. To encourage physical activity, the patients will receive a Garmin activity tracker and will be instructed to wear it all day through the entire study period. The step count is displayed in the LETSGO app when the patient's mobile phone is connected to the activity tracker. Goals will be reviewed and adapted accordingly at subsequent nurse-led visits.

The patients at the intervention hospitals will have access to the LETSGO app throughout the 3-year study period, irrespective of their risk group (except cervical cancer patients in the low-risk group who have been treated with conization only, to avoid unnecessary fear of cancer recurrence in this low-risk population). At the final follow-up visit (at 12 months or 36 months, depending on the risk group), the nurse will emphasize the importance of being attentive to symptoms as signs of recurrence and of a healthy lifestyle for well-being. The patients will receive written information on whom to contact if they experience treatment-related side effects or suspect disease recurrence. A summary of the patient's treatment, potential side effects, and symptoms of potential recurrence will be sent to the patient's responsible general practitioner. The nurses involved in the study are familiar with gynecological cancer patients. They have participated in a 2-day intensive course covering relevant subjects, including gynecological cancer treatment, physical and mental treatment-related symptoms, symptoms of recurrence, benefits of physical activity, autonomous supportive communication style, and motivation and individualized goal setting for physical activity. The nurses' education was reinforced by an electronic learning program with modules covering these subjects, which they were required to complete before the course.

The LETSGO app

The app is available for smartphones and tablets. It contains information on the different gynecological cancers, as well as lifestyle information and advice. It is distributed through Apple Store and Google Play, and a personal code is required to open the study version.
The app consists of the following modules (Figure 1):

1. Disease-specific information (written and audiovisual) on ovarian, uterine, cervical, or vulvar cancer, signs of recurrence, and late effects after treatment.
2. General lifestyle information.
3. Physical activity exercises and programs with instructions (written and audiovisual) for both beginners and experienced persons.

4. Physical activity goal setting: Participants will be asked to define a goal for the week (e.g., a 30-minute walk twice a week or strength exercise in a health studio three times a week).
5. Monitoring of symptoms of recurrence: Once monthly, the participants will be asked to rate 10 symptoms that may indicate recurrence.

Patient-reported outcome studies have shown that the most frequent symptoms of recurrence are pain and fatigue for all gynecological cancers and bleeding for endometrial and cervical cancer [18]. To cover these symptoms, we have selected relevant items from the European Organisation of Research and Treatment of Cancer (EORTC) item library [44], adjusted to each cancer type. The 10 EORTC items in the app refer to the preceding week. For instance, patients treated for endometrial or cervical cancer will be asked, "Have you had abnormal bleeding from your vagina?" Each participant will rate the severity of their symptoms in the preceding week from 0 (not at all) to 3 (very much). If a predefined threshold is reached, the participant will receive an alert on their phone or tablet informing her that the answer given may indicate recurrence and advising her to phone the pre-saved telephone number of the gynecological outpatient clinic. We anticipate that some participants may refrain from making contact. Therefore, the database will be checked for flags at regular time points by the project data manager. Patient visits and imaging will be brought forward if recurrence is suspected.

Control hospitals

Patients will receive standard follow-up according to current guidelines. Standard follow-up in Norway consists of clinical examination with vaginal ultrasound three to four times a year during the first 2 years, twice a year for the next 3 years, and annually thereafter, depending on the recommendations of the patient's doctor.

Data collection

Data will be collected using medical records, patient registries, validated questionnaires (electronic or written), and blood samples. Primary and secondary outcomes will be measured for all participants at enrollment (for baseline data) and again at 3, 6, 12, 24, and 36 months. Biobank samples will be collected at 3, 12, and 36 months and at time of recurrence, if applicable). At each time point, a reminder will be sent within 3 weeks to any participant who does not return the questionnaire. For the intervention group, data will also be abstracted from the app and the activity tracker.

Discontinuation

Participants will be withdrawn from the study if a recurrence occur.

Primary outcome

Patient empowerment

The Health Education Impact Questionnaire (heiQ), a well-validated, widely used measurement system for comprehensively assessing the effects of health education programs on self-management[20, 45]. It consists of 40 questions grouped into eight domains. Responses are given on four-point Likert scales ranging from "strongly agree" to "strongly disagree". The heiQ has been translated into several languages and has been validated in a Norwegian population[46].

Secondary outcomes

Health-related QoL

Health-related QoL will be measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[47] and the EuroQol 5 Dimensions Questionnaire (EQ-5D)[48]. Regarding the EORTC QLQ-C30, the scores of the five functional scales and one global QoL scale are converted to a 0–100 scale [47]. A higher score reflects a better level of functioning and better QoL. Tumor-specific complaints are measured using the disease-specific supplements EORTC QLQ-EN24[49] for endometrial cancer, EORTC QLQ-OV28[50] for ovarian cancer, EORTC QLQ-CX24[51] for cervical cancer, and EORTC VU-34 (under development, phase 4) for vulvar cancer. The EORTC instruments (except EORTC VU-34) have been used in studies of gynecological cancer survivors, some of which were conducted in Norway[14, 15, 52]. The EQ-5D consists of two components: A descriptive system, which defines health-related QoL in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a visual analog scale[48].

Physical activity

Self-reported physical activity will be assessed using the short form of the International Physical Activity Questionnaire (IPAQ-sf)[53]. Exercise stage/readiness to change will be assessed using one item: “Please indicate which alternative corresponds with your current physical activity level or your interest in physical activity.” Responses are given on a five-point ordinal scale from the exercise stages of change assessment instrument[54], which is based on the trans-theoretical (stages of change) model[55]. The scale represents five different stages of change, ranging from 1 = “Not physically active and I do not intend to become more physically active during the next 6 months” (pre-contemplation stage) to 5 = “Physically active and I have been so for more than 6 months” (maintenance stage). Step count data imported from the Garmin activity tracker into the LETSGO app will be compared with self-reports of physical activity.

Fear of cancer recurrence

The Health Worries subscale of the Impact of Cancer (IOC) scale will be used to assess fear of cancer recurrence[56]. The module consists of six questions, including questions on worry about the future, worry about health due to cancer, and worry about recurrence. Items are scored on a five-point intensity scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores reflect greater fear of cancer. The IOC has been validated in oncology patients in oncology settings[56].

Health care utilization

Health care utilization will be assessed by asking patients about the frequency of their contact with their gynecologist and primary care physician and about how many health care visits were related to cancer. We will also assess how often the patients use additional care services (e.g., psychologist, rehabilitation course, physical therapist).

Health economic evaluation

The EQ-5D is the generic measure preferred by the UK National Institute of Health and Care Excellence for cost-effectiveness and comparative purposes, which in turn has affected guidelines in several other countries, including Norway[48]. Quality-adjusted life years (QALYs) will be calculated based on the area-under-the curve principle, taking into account both health-related QoL and

survival of the patients during the 3-year follow-up period. Health care utilization at participating hospitals during the trial will be gathered for both groups. Health care utilization in other parts of the health care sector will be gathered from the following registry data sources: the Norwegian Prescription Database (www.reseptregisteret.no), which contains data on all medical prescriptions redeemed from Norwegian pharmacies; the Norwegian Patient Registry, which includes data on diagnostic information (ICD-10), medical treatment, length of hospital stay, and discharge data; the Municipal Patient and User Register (KPR); the individual-based care and care statistics registry (https://helsedirektoratet.no/iplos-registeret) for variables related to use of specialist and primary health care services; the Control and Payment of Health Reimbursement Database (https://helfo.no/) regarding GP visits, physiotherapy and health transportation; and the social security event database (FD-trygd). The costs of the intervention will be considered along with differences in resource use during follow-up and differences in QALYs to assess the incremental cost-effectiveness of the intervention compared to the control.

Biobanking

Blood samples will be collected at defined time points, as described in Table 1. Standard operating procedures (SOP) have been established for blood and sera collections. The blood samples will be processed in components and stored at −80°C. Three 6 ml EDTA samples will be collected and immediately centrifuged. From these, buffy coat (for isolation of genomic DNA) and plasma (for purification of circulating tumor DNA) will be isolated and stored in cryo tubes. Three SST II 5 ml serum Vacutainers will be collected and centrifuged after 30 min of coagulation time. Serum (for cytokine and metabolite analysis) will then be transferred to cryo tubes for storage. The consented SOP has been introduced at the participating hospitals, with an alternative protocol for the smaller hospitals without microcentrifuges.

Other measurements

Comorbidity will be assessed using the Self-Administered Comorbidity Questionnaire (SCQ) (59), which consists of 16 common and three optional medical conditions. Patients will be asked to indicate whether they have the condition, if they are receiving treatment for it, and if it limits their activities. For the present study, we will only ask whether the patients have any of the common conditions. The SCQ has well-established validity and reliability in Norwegian patients with chronic medical conditions[57, 58]. Demographic information such as age, education, marital status, and treatment will be obtained from baseline questionnaires and medical records.

Sample size calculation

Sample size calculations were based on the primary outcome of interest. From a review of the available literature[46, 59], we anticipated that the change in mean value of the heiQ domain (self-monitoring and insight) from baseline to 12 months would be higher in the intervention group[60]. A 10% difference is considered clinically relevant[61]. Assuming a common standard deviation of 1.4 and using the customary significance level alpha of 5% and power of 80%, we determined that 343 individuals in each group would be needed to reveal a clinically relevant difference of 10% or more. Accounting for a dropout rate of 10%, we determined that 377 would be needed in each group.

Statistical analyses

Data will be analyzed after 1 and 3 years of follow-up. Data will be presented as counts and percentages (categorical variables) and mean and standard deviation or median and range for continuous data following normal or skewed distribution, respectively. Pairs of categorical variables will be compared using a chi-square test or, for small numbers, Fisher's exact test. Univariate analysis for comparison of continuous variables will be performed using a t-test for normally distributed data or the Mann-Whitney Wilcoxon test for variables with skewed distribution. Changes in the main outcome will be analyzed using generalized linear mixed models (GLMM) for repeated measures, as the outcomes are all continuous. As all included individuals will be assessed at several time points (baseline, 3, 6, 12, 24, and 36 months), statistical dependencies will exist. We will adjust for these using an unstructured covariance matrix if the model converges; if the model does not converge, we will fit a more specified covariance matrix. Type of hospital (intervention or reference), time (measurement point), and possible confounders identified when comparing patients at the intervention and control hospitals will be included as fixed factors. To account for added variation caused by enrolling participants at 10 different hospitals, we will include each hospital as a random factor. As GLMM models use all available observations, no imputation of missing data will be necessary. The results will be expressed as estimated means with 95% confidence intervals for each time point and type of hospital (intervention vs. control). Differences in means between the intervention and control groups for each assessment point will be estimated. Time to recurrence will be modeled using survival analysis methodologies. Specifically, we will use Kaplan-Meier curves to depict crude time to recurrence and a Cox model to estimate hazard ratios for recurrence. The economic analyses will include controlling for enrollment differences and sensitivity analyses, according to international guidelines[61].

Committees for the research

A Scientific management group (consisting of the authors of the present protocol paper) has developed this protocol. A steering committee has been appointed to ensure that the trial is conducted in accordance with standard ethical principles. The committee provides an overall supervision of the study regarding the participants' safety, as well the delivery of the project outputs and the achievement of project outcomes.

Data management

The database for clinical data and questionnaire data will be created using the Infodoc software. Data from the app will be stored at Services for sensitive data (University of Oslo). Access to databases will be secured and limited to the professionals involved in the study (personal ID and password required). The investigators in the scientific committee will be given access to the cleaned data set. Data monitoring will be provided by the trial steering committee. The research team will make regular reports to the trial steering committee. Interim analyses and stopping guidelines are not indicated because the intervention is not expected to have a significant risk of potential harm for the patients. The project management group will have close cooperation with project investigators at the participating hospitals. Research nurses at each hospital are responsible for the day-to-day data collection. Collection of data will be supervised by the project management group in close collaboration with the scientific management group.

Patient and public involvement

We appointed a user panel of three women who had been treated for gynecological cancer and had no former experience with mHealth. The users have participated in several meetings since the initial planning of the study, and the resulting follow-up model has been adjusted based on their feedback and opinions. The users have read and commented on the protocol and have been involved in the development of the app. They have given their opinions on both the content of the app and the nurse-led consultations.

Ethics and dissemination

The LETSGO study has been approved by the Regional Committee for Medical and Health Research Ethics of South East Norway (2019/11093). The protocol is registered at www.clinicaltrials.gov (NCT04122235). The institutional review board and the data protection officer at each of the study sites have also approved the study. All patients will receive oral and written information about the study, and written informed consent will be collected prior to enrollment. An electronic case report form is used, and participants receive a unique subject number and subject identifier. Data are entered under this identification number onto a central database stored on secured servers. The servers are protected by firewalls and are patched and maintained according to best practice. The study investigators retain the right to access data. It is estimated that the study will be completed in 2024, after which the data analysis and the results will be disseminated.

Trial status

The trial started inclusion in November 2019. On 27 May 2021, 378 patients have been included.

Authors' contributions: IV, SB and ID conceived the study in collaboration with the other authors. IV was responsible for writing the protocol. M Skorstad, M Småstuen, KL, TW and LPF provided critical feedback during the conception of the study and the writing up of the protocol.

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Competing interest statement: None declared.

Figure Legend:

Figure 1. The LETSGO-app (©Anette Gjoerv)

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Table1. Overview of all outcome measures and assessment times of the LETSGO study

Outcomes	Measurement instrument	Intervention hospitals										Control hospitals								
		B[1]	3w[2]	6w	3m[3]	6m	9m	12 m	15 m	18 m	21 / 30 m	24 / 36 m	B	3m[4]	6m	9m	12 m	15 m	18 m	21/ 30 m	24/ 36 m
Questionnaires																					
Psychosocial outcomes																					
Patient empowerment	heiQ[6]	X			X	X		X				X	X	X	X		X				X
Generic QOL[5]	EQ-5D[7]	X			X	X		X				X	X	X	X		X				X
Disease specific QOL	EORTC QLQ-C30[8]	X			X	X		X				X	X	X	X		X				X
Tumor specific QOL	EORTC QLQ modules[9] CX24,	X			X	X		X				X	X	X	X		X				X
	EN24, OV28 and VU34	X			X	X		X				X	X	X	X		X				X
Cancer worry	IOC[10] worry subscale	X			X	X		X				X	X	X	X		X				X
Sexuality	SQOL-f[11] selected items	X			X	X		X				X	X	X	X		X				X
Follow-up care	Study-specific questions	X			X	X		X				X	X	X	X		X				X
Personal factors																					
Demographic variables	Standard questions	X			X	X		X				X	X	X	X		X				X
Comorbidity	SCQ[12]	X			X	X		X				X	X	X	X		X				X
Lifestyle factors	IPAQ-SF[13], ESAI[14]																				
Physical activity	Standard questions	X			X	X		X				X	X	X	X		X				X
Alcohol use	Standard questions	X			X	X		X				X	X	X	X		X				X
Smoking		X			X	X		X				X	X	X	X		X				X
Clinical factors	eCRF[15]																				
Medical history	eCRF	X											X								
Medication	Blood pressure, pulse,	X											X								
Vital signs	weight	X		X		X		X		X		X									
Performance status	ECOG[16] status	X		X		X		X		X		X									
Gynecological examination	NA[17]				X		X		X		X			X	X	X	X	X	X	X	X
LETSGO intervention (nurse)																					
Introduction to LETSGO-app	NA			X		X		X		X		X									
Assessment of rehabilitation needs	NA			X		X		X		X		X									

Set goals for physical activity	NA			X																
Follow up goals for physical activity	NA					X		X		X		X								
Motivating interview	NA	X		X		X		X		X		X								
Assessment of late-effects	Study-specific chart					X		X		X		X								
Visits at out-patient clinic	NA																			
Low risk group intervention		X	X		X		X													
Medium/high risk group intervention		X	X		X		X		X		X									
Control group (all)													X	X	X	X	X	X	X	X
Biological factors																				
General laboratory	Blood	X			X	X		X				X	X	X	X		X			X
Biomarkers	Blood				X			X				X[18]	X	X			X			X[18]

[1]Baseline; [2]Weeks; [3]Months; [4]At reference hospitals, first questionnaire/blood tests may be collected at 3 months; [5]Quality of Life; [6]Health Education Impact Questionnaire; [7]EuroQol 5 dimensions questionnaire; [8]The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; [9]Modules: cervix, endometrium, ovarian, vulvar; [10]The Impact of Cancer Questionnaire; [11]Sexual Quality of Life–Female Questionnaire; [12]Self-Administered Comorbidity Questionnaire; [13]Physical Activity Questionnaire Short-Form [14]Exercise Stage Assessment Instrument; [15]Electronic Case Report Form; [16]Eastern Oncology Cooperative Group; [17]Not applicable; [18]Biomarkers at 3, 12 and 36 months.

Figure 1. The LETSGO-app (☐Anette Gjoerv)

1292x849mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary
Protocol version	3	Date and version identifier	Supplementary
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 10
	5b	Name and contact information for the trial sponsor	Supplementary
	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	Supplementary
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

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	3, 4
	6b	Explanation for choice of comparators	4, 7
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
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	5
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)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6, 7
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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	7, 8, 9
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)	5,7

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5, 6
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	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5, 7, 8, 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6, 9

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	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	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	10
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	Supplementary

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
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	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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	Appendix

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04122235
Date of registration in primary registry	09.02.2019
Secondary identifying numbers	REC 2019/11093
Source(s) of monetary or material support	The Norwegian Cancer Association The UNI foundation The South-Eastern Norway Regional Health Authorities The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results
Primary sponsor	Hospital of Southern Norway The sponsor had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results
Contact for public queries	Ingvild.vistad@sshf.no
Contact for scientific queries	Ingvild Vistad MD, Hospital of Southern Norway
Public title	The LETSGO study
Scientific title	Lifestyle and Empowerment Techniques in Survivorship of Gynecologic Oncology (LETSGO study). A multicenter longitudinal intervention study using mobile health technology and biobanking.
Countries of recruitment	Norway
Health condition(s) or problem(s) studied	Follow-up of gynecological cancer patients
Intervention(s)	Partly nurse-led follow up with an emphasis on self-management and physical activity versus traditional follow-up
Key inclusion and exclusion criteria	Inclusion criteria: (1)histologically verified cervical cancer (restricted to squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), endometrial cancer, ovarian cancer (restricted to epithelial type), or vulvar cancer; (2) scheduled for follow-up after completed primary standard treatment; (3) able to complete patient-reported outcome measures independently in Norwegian; (4) ≥ 18 years; and (5) able to provide informed consent. Exclusion criteria: (1) participation in a clinical treatment trial; (2) ongoing intravenous maintenance treatment (e.g., bevacizumab); (3) cervical cancer patients treated with trachelectomy.
Study type	Quasi-experimental multicenter clinical study with intervention hospitals and control hospitals
Date of first enrolment	November 2019
Target sample size	754
Recruitment status	Recruiting
Primary outcome(s)	Patient empowerment
Key secondary outcomes	Health-related QoL; physical activity; health economy; changes in biomarkers

Protocol version

Date	Original
12.02.19	Amendment #1 Added one investigator.
14.09.19	Amendment #2 Correction of typographical errors in tables
09.10.19	Amendment #3 Blood tests at recurrences. Specification of inclusion/exclusion criteria (patients on *intravenous maintenance therapy* cannot be included)
22.10.19	Amendment #4 More detailed information on budget
30.10.19	Amendment #5 Outcome regarding biomarkers moved from secondary to tertiary outcome
06.11.19	Amendment #6 Correction of typographical errors
09.12.20	Amendment #7 Enrollment date adjusted. Removed Erythrocyte sedimentation rate from the blood tests. Emphasized that the LETSGO-app will not be uninstalled in low-risk group at 12 months. Sexuality added as secondary outcome. Added information on questionnaires used for evaluating physical activity, fear of recurrence of cancer and sexuality.