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Clinical Trial Protocol

Study protocol for two stepped-wedge interventional trials evaluating the effects of holistic information technology-based patient-oriented management in older multimorbid patients with cancer: The GERONTE trials

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ABSTRACT

Introduction: Current hospital-based care pathways are generally single-disease centred. As a result, coexisting morbidities are often suboptimally evaluated and managed, a deficiency becoming increasingly apparent among older patients who exhibit heterogeneity in health status, functional abilities, frailty, and other geriatric impairments. To address this issue, our study aims to assess a newly developed patient-centred care pathway for older patients with multimorbidity and cancer.

The new care pathway was based on currently available evidence and co-designed by end-users including health care professionals, patients, and informal caregivers.

Within this care pathway, all healthcare professionals involved in the care of older patients with multimorbidity and cancer will form a Health Professional Consortium (HPC). The role of the HPC will be to centralise oncologic and non-oncologic treatment recommendations in accordance with the patient's priorities. Moreover, an Advanced Practice Nurse will act as case-manager by being the primary point of contact for the patient, thus improving coordination between specialists, and by organising and leading the consortium. Patient monitoring and the HPC collaboration will be facilitated by digital communication tools designed specifically for this purpose, with the added benefit of being customisable for each patient.

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Materials and Methods: The GERONTE study is a prospective international, multicentric study consisting of two stepped-wedge trials performed at 16 clinical sites across three European countries. Each trial will include 720 patients aged 70 years and over with a new or progressive cancer (breast, lung, colorectal, prostate) and at least one moderate or severe multimorbidity. The patients in the intervention group will receive the new care pathway whereas patients in the control group will receive usual oncologic care.
Discussion: GERONTE will evaluate whether this kind of holistic, patient-oriented healthcare management can improve quality of life (primary outcome) and other valuable endpoints in older patients with multimorbidity and cancer. An ancillary study will assess in depth the socio-economic impact of the intervention and deliver concrete implementation guidelines for the GERONTE intervention care pathway.
Trial registration: FRONE: NCT05720910
TWOBE: NCT05423808

1. Background

By 2040, the average life expectancy in Western Europe is estimated to increase to over 85 years [1]. Ageing is a heterogenous process resulting in significant variation regarding physiological, emotional, psychological, and social health. Older people have an increased prevalence of co-occurring acute or chronic diseases [2], generally defined as multimorbidity [3,4], that can reduce quality of life, impair health outcomes, and cause a significant disease burden and increased risk of death [5–8].

Cancer prevalence also increases with age. As a result, the number of older persons with cancer is expected to increase significantly as the proportion of older people rises in societies [9]. Treatment of cancer in this population is complicated; older patients have often been underrepresented in clinical oncology trials [10–12] and treatment guidelines often fail to take multimorbidity into account. The complex health status of these patients requires an oncologic decision-making process that considers the overall health status of the patient and their personal priorities. For this, geriatric assessment (GA) has been proven to be necessary and beneficial, and increasing evidence demonstrates the benefit of GA-guided treatment decisions in optimising outcome of oncologic treatment in older patients [13]. To deal with the increasing number of multimorbid patients, healthcare systems will require an organisational shift from single-disease-centred to patient-centred care pathways, involving multidisciplinary medical and paramedical collaboration [14,15]. For older patients with multimorbidity and cancer, further innovative comorbidity management strategies are needed to support both patients and their caregivers in self-management [16]. Novel information and communication technologies (ICT) provide interesting opportunities for such innovations, broadening the spectrum of interaction options and information exchange between patients and their healthcare providers.

The GERONTE project [17] is a five-year Horizon 2020 research and innovation project funded by the European commission with the overall aim to improve quality of life for older patients with multimorbidity and cancer, while reducing the overall costs of care. GERONTE stands for Streamlined Geriatric and Oncologic evaluation based on IC Technology for holistic healthcare management for older multimorbid patients.

The first phase of the GERONTE project focused on developing a new care pathway for older patients with multimorbidity and cancer, which addressed the main challenges healthcare professionals and patients themselves experience in their oncologic care trajectory [18]. These included issues relating to coordination of care and communication; choosing the most suitable treatment for an older patient; enhancing the inclusion of non-oncologic information in shared decision-making; maintaining quality of life and functional state during and after treatment; and finally monitoring and dealing with symptoms, side-effects, and interactions between multimorbidity and cancer (both the disease process and its treatment) [18].

The process of the development of the new care pathway – including co-design with and by patients, informal care-givers, and healthcare professionals – was described in detail elsewhere [19]. The main components are shown in Fig. 1. At the heart of the care pathway are all relevant healthcare professionals for the individual patient, including at least a cancer specialist, the geriatrician, and preferably, the primary care physician, united in a healthcare professional consortium (HPC) assisted by an advanced practice nurse (APN) and supported by digital tools consisting of a patient application and a health care professional dashboard. The HPC will centralise the cancer treatment recommendations based on oncologic data as well as detailed information regarding the patient's health status derived from a comprehensive geriatric assessment (CGA) and will align their treatment recommendations to the patient's priorities. Supporting digital tools have been developed for both healthcare professionals and patients. For involved healthcare professionals, a dashboard will provide a structured presentation of patient and tumour information during decision-making, treatment, and follow-up. For patients, a symptom-monitoring application will allow for ongoing monitoring of cancer-related symptoms, side-effects, signs of destabilized comorbidity, and/or functional decline, with a self-management library containing recommendations on how to deal with issues and when to contact their healthcare professionals in case of symptoms requiring urgent intervention. The HPC will provide recommendations for non-oncologic interventions aimed at optimising the patient's health status throughout the treatment trajectory and subsequent recovery. The APN forms the primary contact point in the coordination of the patient's healthcare in general, with regular consultations for advice or coaching as needed, and will actively involve patients and their caregiver in the care trajectory.

The second phase of the GERONTE project consists of testing the effectiveness of this new care pathway in clinical practice by performing two prospective randomised clinical trials, one in France (FRONE) and one in Belgium and the Netherlands (TWOBE). In this paper of the GERONTE project, we will describe the design and methodology protocol of both clinical trials.

2. Methods

2.1. Aims

The aim of the GERONTE clinical trials (FRONE, TWOBE) is to assess the effectiveness of the GERONTE care pathway compared to standard oncologic care for older patients with multimorbidity in three different countries (France, Belgium, Netherlands).

The primary objective is to examine the impact of the GERONTE care pathway on six-month health-related quality of life (HRQoL) in older patients with multimorbidity and cancer. Secondary objectives are to evaluate whether the GERONTE care pathway can improve quality of life throughout the first year, as well as improve anxiety, autonomy, caregiver burden, and survival and reduce unplanned hospitalisations and patient institutionalisation. Patient and healthcare professional experience and satisfaction with the GERONTE care pathway will also be assessed. Additionally, the clinical trial will assess the cost-utility and cost-effectiveness of the GERONTE care pathway versus standard care up to one-year post-inclusion.

An ancillary study will explore the implementation journey with a specific focus on identifying, describing, analysing, and mapping the common and distinctive elements of the current care pathways for older patients with multimorbidity (with cancer as a primary condition) within each clinical site involved prior to the implementation of GERONTE. Additionally, it will also describe and analyse the process of implementation of the intervention in the trial sites, going beyond the specific trial outcomes. This broader analysis will provide insights into the mechanism of action of the intervention, the contextual factors, and barriers and facilitators to implementation. The ultimate goal is to develop a comprehensive implementation guide that will inform implementation of GERONTE across various settings.

2.2. Ethics Approval

For France, authorisation for the clinical trial was obtained by L'Agence Nationale de Sécurité du Médicament et des produits de Santé (ANSM) and les Comités de Protection des Personnes (CPP); autorisation from the Commission Nationale de l'Informatique et des Libertés (CNIL) is pending.

In Belgium, ethics approval was obtained by a consolidated opinion of Federal Agency of Medicines and Health Products (FAMHP) and an independent Ethics Committee.

In the Netherlands, the clinical trial was approved by the Medical Research Ethics Committees United (MEC-U). Additional local approval is required for the four participating Dutch centres before the clinical trial can commence.

2.3. Design and Setting of the Study

This is a prospective international, multicentric study consisting of two stepped-wedge cluster randomised clinical trials in two different European geographical areas, FRONE in France and TWOBE in Belgium and the Netherlands. Each trial will be conducted in eight hospitals (eight French centres for FRONE; four Belgian and four Dutch centres for TWOBE; both academic and community hospitals will be included). The two trials will be identical regarding the study design, randomisation, intervention, and follow-up.

In the stepped-wedge clinical trial design, all eight centres will start in the control arm for two months. Subsequently, one centre will switch to the intervention arm every two months and will remain in this arm until the end of the trial. By the end of the 18-month inclusion period, all centres will have switched to the intervention arm and have included patients in this arm for at least two months (Fig. 2). After inclusion, individual patients will remain in the arm they were assigned to and will be monitored for 12 months.

The order in which centres will switch from the control arm to the intervention arm has been randomised prior to the start of the research using SAS software (version 9.4). Unconstrained randomisation was performed for each of the two trials independently.

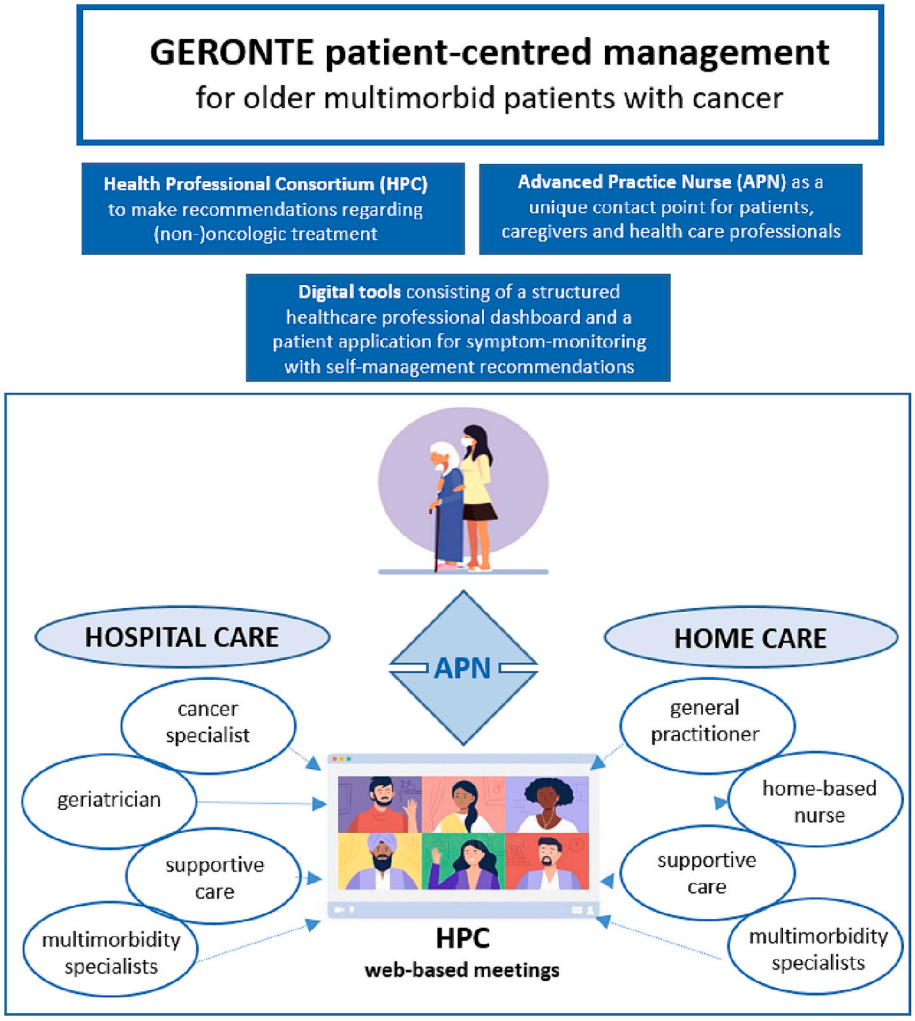

Fig. 1. Main components of the GERONTE patient-centred management.
APN advance practice nurse, HPC health care professional consortium.

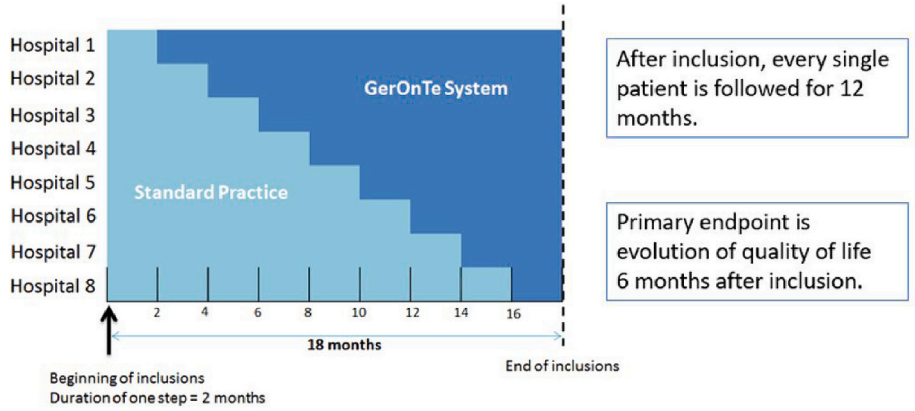

Fig. 2. Stepped-wedge clinical trial design.

Blinding is not feasible due to the nature of the intervention. Thus, neither participants, cancer specialists, geriatricians, nor other health-care professionals will be blinded to allocation. There will also be no blinding of the statistical team.

2.4. Eligibility Criteria

2.4.1. Inclusion criteria

Candidates for inclusion are patients aged 70 years and over with a new or progressive cancer fulfilling specific tumour criteria, where a new treatment option is considered that is potentially burdensome for older patients, and having at least one moderate or severe comorbid condition. The cancer types included are breast, lung, colorectal, and prostate cancer, and disease can be non-metastatic or metastatic. For each cancer type, multidisciplinary input was obtained to determine which treatment types should be considered as potentially burdensome; low-impact treatment options were not included as the benefit of the GERONTE care pathway is likely to be too limited. Web appendix 1 lists the tumour-specific inclusion criteria per tumour type and stage, as well as the criteria for treatments that are potentially burdensome. Patients will be recruited by the oncologist (potentially with support of a research nurse); if recruitment takes place prior to the multidisciplinary tumour board (MTB), potential treatments will be judged based on standard care and the clinician's assessment.

In addition to one of the four cancer types, patients must have at least one moderate/severe comorbidity, other than the current cancer, to be labelled as a patient with multimorbidity. To develop these criteria (Web appendix 2), the first step was to identify all grade 3–4 criteria from the Cumulative Illness Rating Scale-geriatric version (CIRS-G) [20] and grade 2–3 criteria from the Adult Comorbidity Index (ACE)-27 [21]; subsequently, criteria were combined or rephrased to simplify the list. Based on expert input from cancer specialists and geriatricians involved in geriatric oncology, additional criteria were formulated to incorporate geriatric impairments and non-organ specific issues that contribute to multimorbidity.

To be eligible for inclusion, patients must have a life-expectancy of at least six months (based on clinical judgement) and must have completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [22] Quality of Life Questionnaire during the screening period, prior to inclusion. Finally, patients must be willing and able to comply with study procedures and must voluntarily provide written informed consent.

For participation in the FRONE trial, patients must also be affiliated with a French social security scheme in accordance with the French law on biomedical research (Article 1121–11 of the French Code of Public Health [23]).

2.4.2. Exclusion criteria

Patients will be excluded if they have a mental illness or cognitive impairment that limits their ability to provide consent or complete trial procedures; if they are already participating in an interventional clinical trial with a non-registered anticancer drug or in a geriatric intervention trial; or if they and their caregivers are unable or unwilling to use ICT devices.

2.5. Sample Size Determination

The intervention will be considered successful if a mean difference of 10 points or more (on a score of 0–100) at six months could be detected for at least one of three targeted HRQoL scores (global health status score, physical functioning scale, emotional functioning scale) of the QLQ-C30 [22]. Each of the three scales will be tested independently. To be able to detect this difference, to account for this multiple outcome criterion, and to be conservative regardless of the alpha risk adjustment method used, the 5% type 1 error is shared between the three criteria. Thus, with a two-sided type I error of 1.6% and statistical power of 90%, an individual trial would need to include 222 patients. Factoring a possible drop-out rate of 20%, the minimum total number of patients to be included would be 278 for an individual randomised trial. Accounting for the effect of the stepped-wedge study design, with an intra-cluster correlation coefficient of 10% and eight centres included, the number of patients to be included is 720, which corresponds to 10 patients per step of two months per centre for both clinical trials [24].

2.6. Recruitment

Patients will be recruited among inpatients and at out-patient clinics of the participating centres. Each centre is expected to recruit 90

Table 1
Patients in control and intervention arms per step for clinical trials FRONE and TWOBE.

Randomised investigating sites	Number of patients to include per step	Total number of patients to include Control arm	Total number of patients to include Intervention arm	Total number of patients to include – Per site
Hospital 1	10	10	80	90
Hospital 2	10	20	70	90
Hospital 3	10	30	60	90
Hospital 4	10	40	50	90
Hospital 5	10	50	40	90
Hospital 6	10	60	30	90
Hospital 7	10	70	20	90
Hospital 8	10	80	10	90
Total	80	360	360	720

patients; distribution across the intervention and control arms will vary depending on their moment of switching to the intervention arm (Table 1). While the possibility of not achieving the minimum of 10 patients per two months on a rare occasion is factored into the dropout rate of 20%, all centres were required to assess their capacity to recruit sufficient participants before joining the study. This ensures a sufficient sample size for each two-month period maximizing the power of the statistical analyses. It is important to note that recruiting more than 10 patients in a two-month period does not pose issues for the analyses, but these additional patients will not be covered by the available funding.

Centres do not have to include patients of all cancer types in order to participate in the trial. However, a certain level of homogeneity throughout the inclusion period is essential. For example, if a centre is initially not able to include patients with colorectal cancer because of an overlapping geriatric intervention trial for that cancer type, then this should remain so throughout the duration of the GERONTE project, even if the overlapping trial has ended.

For the ancillary study, approximately 3–5 staff members (e.g.,

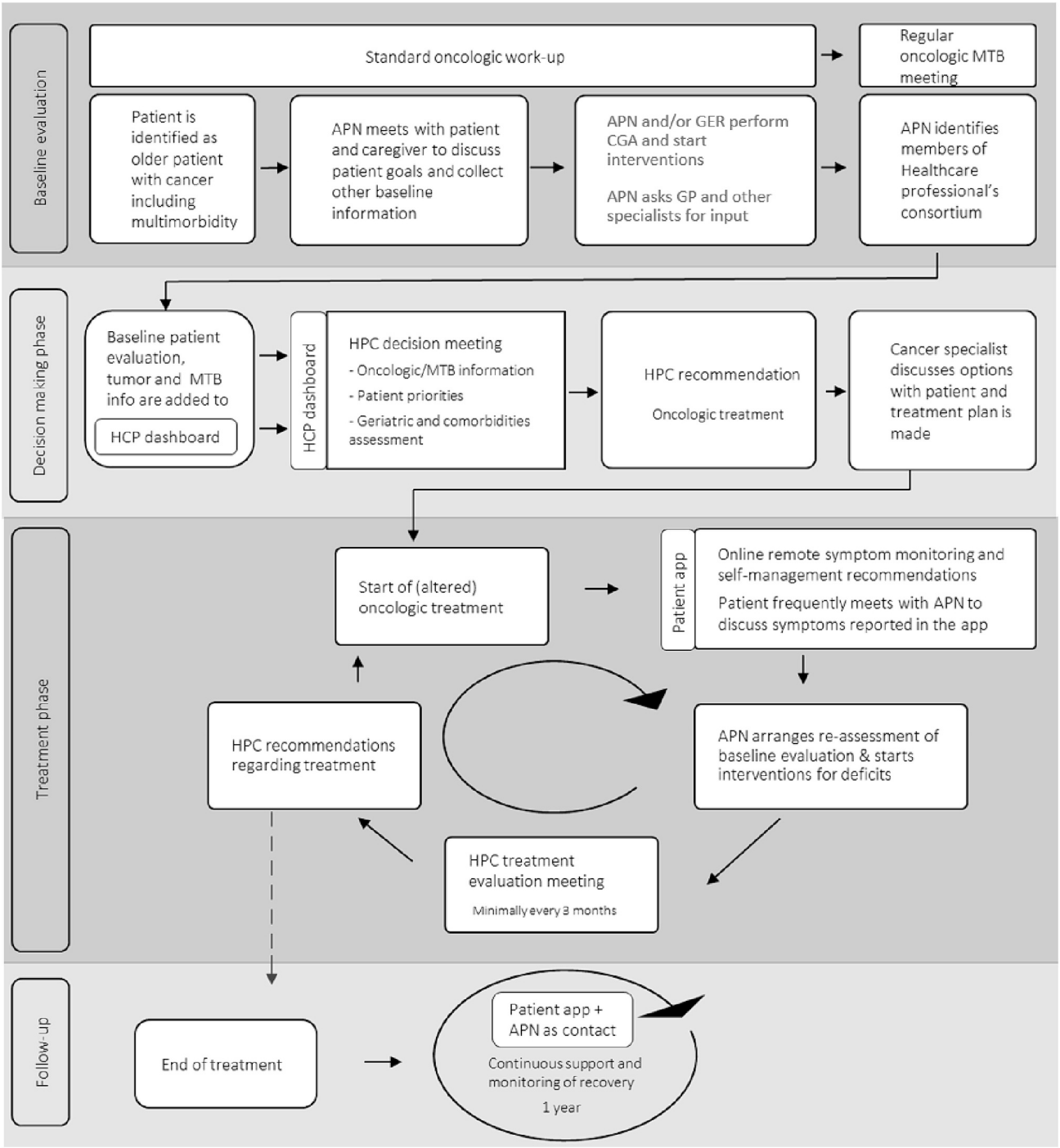

Fig. 3. Details of the GERONTE care pathway.
Schematic overview of GERONTE pathway and its most important components.
APN; advanced practice nurse, GER; geriatric expert, CGA comprehensive geriatric assessment GP; general practitioner, HCP; healthcare professional, HPC; healthcare professionals consortium, MTB; oncologic multidisciplinary tumour board.

principal investigator, clinicians, nurses, administrators) and 5–10 patients and/or informal caregivers per participating centre will be included over the entire duration of the project.

2.7. Description of the Intervention and Control Arms

2.7.1. Intervention arm

The intervention will consist of the GERONTE care pathway [19]. The various steps are summarised in Fig. 3, showing at which time points each of the following components come into play.

A *health professional consortium (HPC)* will be composed for each patient based on the needs of their specific situation, consisting at minimum of a cancer specialist, a geriatrician, and an *advanced practice nurse* (APN). The APN will identify who should be included in the HPC, coordinate the HPC meetings, and gather input from other healthcare professionals (medical and/or paramedical; hospital- and/or community-based) if these professionals are not able to join the HPC themselves.

The HPC members will come together to make recommendations regarding oncologic treatment and non-oncologic interventions at baseline and during the course of treatment, using a standardised decision-making checklist developed specifically for this purpose [25]. This will be in addition (before or after) to the usual multidisciplinary tumour board (MTB) which provides oncologic treatment recommendations based on the usual oncologic work-up. HPC recommendations will subsequently be discussed with the patient in shared decision-making with their cancer specialist and implemented accordingly. Follow-up HPC meetings will take place every three months, but additional HPC meetings can be planned as needed.

In addition to coordination of the HPC, the APN will have a central role as the first point of contact for the patient. The APN will collect additional information regarding patient's social situation, priorities, and preferences, will monitor patients during treatment, and will initiate non-oncologic interventions based on the recommendations of the HPC.

A *baseline patient evaluation* will consist of a CGA by a geriatrician (potentially supported by the APN, depending on local practice) which will focus on general health status, comorbidities, and frailty/intrinsic capacity [26]. This will include detailed information on the patient's social situation, comorbidities and medication use, intrinsic capacity/frailty, and non-cancer related prognosis. No standardized set of tools was defined for the CGA as it was felt that feasibility of trial participation would benefit from allowing centres to build on existing local practices. Instead, a list was developed of geriatric domains to be included and a standardized way of reporting of assessment results [26], leaving the responsibility of the assessment methodology to the individual oncology teams [27].

A *healthcare professional dashboard* will provide a structured presentation of patient and tumour information, both during the decision-making phase as well as during treatment and follow-up, according to a standard consensus-based dataset. Details regarding the process of developing the dashboard and rationale for included items can be found in the online GERONTE repository [25]. Dashboard data are shown in Table 2; these will be made available to all members of the HPC involved for in the care for the individual patients.

A *patient application* will allow for ongoing patient monitoring, which can be reviewed on the healthcare professional dashboard. The application provides a self-management library, which combines recommendations relating specifically to cancer- and/or cancer-treatment-related issues as well as problems relating to comorbidities and geriatric impairments. The application also contains specific instructions on when to contact their health care provider; the primary point of contact will be the APN who will assess what is needed and refer to a specialist if necessary.

For patients without access to an ICT device such as a smartphone, tablet, or computer (estimated to be 10% of the patients), a tablet with internet subscription will be provided free of charge for the duration of the study. If needed, patients with limited ICT device experience or cognitive symptoms are allowed to be assisted by an informal caregiver

Table 2
Overview of the components of the health care professional dashboard and patient application.

Health care professional dashboard
Items for the decision-making phase

- Personal data (including primary caregiver and general practitioner information),
- Information about the living and social situation,
- Tumour-related data based on a minimal oncologic dataset, including MTB recommendations,
- Information about comorbidities including severity and impact on daily life,
- Information about prognosis (non-cancer related),
- Outcome of the intrinsic capacity/frailty evaluation performed by the geriatrician,
- Patient priorities and preferences,
- Patient decision control preferences,
- Information about medication and allergies,
- Input from other healthcare professionals,
- Decision-making checklist and report.

Additional items for the follow-up phase

- Symptom monitoring information from the patient application,
- Patient's questions for the APN or HPC,
- Oncologic and non-oncologic treatment
- Hospitalisations,
- Overview of past and future HPC meetings.

Patient application

- Symptom monitoring tailored to the tumour type and treatment; the frequency with which symptoms are monitored varies from daily to monthly, depending on how likely they are to fluctuate and the treatment phase (active treatment or follow-up) [47],
- A self-management recommendation library with prioritisation for reported symptoms,
- A warning system for patients to contact their medical team in case of severe symptoms including emergency numbers, in and out of office hours,
- History of symptoms,
- Section for preparing the next consultation including standard question lists developed specifically for this purpose [48],
- The possibility to set up reminders for completing the symptom monitoring.

MTB; oncologic multidisciplinary tumour board, APN; advanced practice nurse, HPC; health professionals consortium.

in the use of the applications.

Components of the patient application are listed in Table 2.

2.7.2. Control arm

Patients in the control arm will receive oncologic care as usual. These data will be collected by a research nurse.

2.8. Assessments

Table 3 provides an overview of all the evaluations throughout the clinical trial for both the control arm and the intervention arm.

2.9. Primary Outcome Measure

For the primary endpoint, the global health status score, physical functioning subscale, and emotional functioning subscale of the EORTC QLQ-C30 (version 3.0) [22] questionnaire will be analysed independently. The normalised score will be calculated for the three subscales with EORTC manual. The principle for scoring is: estimate the average of the items that contribute to the subscale to obtain the raw score and use a linear transformation to standardise the raw score on a scale of 0 to 100 [28]. The GERONTE intervention is considered effective in case of a ten-point or greater positive difference in health-related quality of life at six months on one or more of these subscales between control group and intervention group.

2.10. Secondary Outcome Measures

All secondary analyses will take place at baseline 3, 6, 9, and 12 months unless stated separately.

2.10.1. Quality of life

Secondary quality of life outcomes include:

- Normalised scores of global health status, physical functioning scale, and emotional functioning scale of the QLQ-C30 (version 3.0) questionnaire collected at baseline, 3, 9, and 12 months.
- Normalised scores of the remaining following QLQ-C30 subscales/items: role functioning, cognitive functioning, social functioning, fatigue, nausea, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties.
- Scores on the following QLQ-ELD14 subscales/items [29]: mobility, worries about others, future worries, maintaining purpose, burden of illness, joint stiffness, and family support. This is a complementary module to the QLQ-C30 that takes into account the specific needs of older patients.

2.10.2. Survival

Survival analyses will include overall survival at 12 months and progression-free survival defined as the time from study treatment initiation to the first occurrence of disease progression or death (by any cause), whichever occurs first.

Table 3
Overview of clinical trial assessments.

	Screening D-28 to D-1	T0 Baseline/ Inclusion	T3 (3 months ±3 weeks)	T6 (6 months ±3 weeks)	T9 (9 months ± 3 weeks)	T12 (12 months ± 3 weeks)
Evaluations included in both study arms						
Written informed consent**	X					
Checklist of eligibility criteria**	X					
Medical history, baseline conditions including comorbidities, signs, and symptoms**		X				
Performance status (ECOG-PS)**		X	X	X	X	X
Concomitant medications**		X				
Demographic data (sex, age, height, weight at baseline, then only weight) **		X	X	X	X	X
Cancer information (diagnosis of the primary disease, prior and current cancer treatments)**		X	X	X	X	X
Quality of life (EORTC QLQ-C30)*	<--------X------>		X	X	X	X
Quality of life (EORTC QLQ-ELD14)*		X	X	X	X	X
Overall health status (EQ-5D-5L)*		X	X	X	X	X
Autonomy (Katz ADL, chair stand test, clinical frailty)**		X	X	X	X	X
Anxiety and depression (HADS)*		X	X	X	X	X
Patient caregiver Information**		X	X	X	X	X
Patient general practitioner contact information**		X				
Worth of treatment*				X		X
Unscheduled hospitalisations**		<----------X---------->				
Patient institutionalisation**		<----------X---------->				
		<----------X---------->				
Patient experience (P3CEQ)*				X		X
Resource use (direct and indirect costs) */**		X	X	X	X	X
Intention to use (modified version of MAUQ)*				X		X
Additional evaluations and trial procedures in intervention arm						
Patient application completion*						
APN consultation + assessments		X				
Comprehensive geriatric assessment as usual site procedures**		X				
Ancillary studies**		<----------X---------->				

ECOG PS Eastern cooperative oncology group performance status; EORTC European Organisation for Research and Treatment of Cancer; QLQ quality of life questionnaire; HADS hospital anxiety and depression scale; P3CEQ Person-Centred Coordinated Care Experience Questionnaire; MAUQ mHealth App Usability Questionnaire; APN advance practice nurse.

* Self-administrated questionnaires.

** Questionnaires and tests conducted by a study collaborator.

2.10.3. Patient autonomy, frailty, anxiety, and weight evolution

The following patient-centred outcomes will be evaluated:

- Dependence score of the Activities of Daily Living (Katz ADL) [30]
- Proportion of patients living at home at 6 and 12 months
- Time to complete five chair stands [31]
- Score of the Clinical Frailty Scale [32]
- Performance status (Eastern Cooperative Oncology Group [ECOG])
- Weight evolution
- Score of Hospital Anxiety and Depression [33]

2.10.4. Patient institutionalisation and unscheduled hospitalisations

These analyses will include the proportion of patients institutionalised at baseline, 6, and 12 months, the proportion of patients with at least one unscheduled hospitalisation, and the number of unscheduled hospitalisations per patient during 12 months after inclusion.

2.10.5. Cost-utility and cost-effectiveness analysis

The primary cost-effectiveness and cost-utility evaluation will be conducted from a societal perspective, which accounts for both the costs from the public payer perspective as well as other direct and indirect costs relevant for different stakeholders, including patients (e.g., transportation, formal and informal caregiver time and/or productivity losses, out-of-pocket expenses, or co-payments). A secondary analysis will additionally be conducted from the payer perspective only, with the aim of estimating the budgetary impact on public finances. In this case, only the resources used within the hospital setting will be considered. Unitary costs of patient services (e.g., cost per bed day or cost per outpatient visit or informal care costs) will be obtained from public data sources. A map of available patient-level real-world data in each country will be created to generate real-world evidence.

Results will be presented as the cost per life years gained in the cost-effectiveness analysis and the cost per quality adjusted life years (QALYs) gained in the cost-utility analysis. Incremental cost-effectiveness ratios will be calculated as the difference in costs between the intervention and the comparator divided by the difference in benefit. Life years gained will be derived from a clinical metric (overall survival/progression-free survival) that will be measured at 6 and 12 months. QALYs will be calculated using utility values derived from normalised scores of EQ-5D-5L questionnaire [34].

Resource use data during the 12 months of patient follow-up will include all direct costs, both healthcare-related and non-healthcare-related, and indirect costs. Direct healthcare costs include hospital-based services, pharmaceutical consumption, emergency department use, outpatient care, and any costs relating to the intervention; direct non-healthcare costs include travel expenses and consumption of community/professional care. Indirect costs include caregiver production loss and unpaid caregivers' labour (informal care). These data will be collected through:

- Trial case report forms completed by the study collaborator or the APN
- Electronic medical records and electronic patient files linked to the patient sample by deterministic matching
- Patient questionnaires on the frequency of visits to the medical specialist, APN, general practitioner
- Caregiver questionnaire for the estimation of costs of informal care and productivity losses

2.10.6. Caregiver burden in health, psychological well-being, finances, social life, and relationship with patient

Total burden will be obtained using the Zarit Burden Interview [35].

2.10.7. Patient-reported overall experience of person-centred coordinated care

Patient experience will be measured through the Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) [36] and a question about how worthwhile the treatment was to the patient, both at 6 and 12 months.

2.10.8. Patient, physician, and healthcare professional-reported overall satisfaction with GERONTE ICT

For patients, physicians, and other healthcare professions, satisfaction and usability of the ICT-application within the GERONTE intervention will be evaluated by using the score derived from the 21-items mHealth App Usability Questionnaire (MAUQ) [37] for stand-alone mHealth Apps at 6 and 12 months. There are specific versions for patients and for healthcare professionals.

2.11. GERONTE Patient-Centred System Implementation and Usage

The following items will be used to assess GERONTE implementation and usage at 6 and 12 months:

- Number and frequency of connections to the patient application
- Duration of logins and activities with the patients
- Number of web-based meetings with APN by site
- Number of APN consultations by site (and by patient) and kind of interventions/actions taken
- Number of patient-related outcome questionnaires completed by patient
- Number of Health Professional Consortium (HPC) meetings with complete dashboard analysis by site
- Number of health professional meetings (Multidisciplinary Tumour Boards (MTB) or other morbidities treatment decision) involving complete dashboards analysis by site

3. Statistical Analysis

3.1. Data Management

The data will be collected on a password-protected electronic Case Report Form (eCRF) and secure database using online trial management software (Macro version 4, Infermed Company). The database is hosted on a server at the Institut Bergonié in Bordeaux, France.

3.2. Data Analysis

The main analysis will be performed in intention-to-treat (ITT) analysis, i.e., all participants will be included in the analysis in the group to which they were initially allocated and all their data is used, regardless of protocol deviations during the trial. The planned date of intervention implementation will be used to classify participants into the control and intervention arms. Missing data will be replaced using multiple imputation. Since the primary endpoint is a QOL score, replacement of missing data will be done as follows:

- For dead patients, QOL at six months will be put at 0.
- At the global score level in the case of a number of missing items greater than 50%.
- At the item level when the number of missing items in the dimension is less than 50%.

In a second step and in order to check the robustness of the results, secondary (under-treatment, per-protocol) and sensitivity for missing data ("missing = failure", complete-case) analyses will be performed.

Descriptive analyses will be presented overall and by intervention group. All comparisons will be performed with a type I error of 5%.

3.2.1. Analysis of the primary end-point

The primary endpoint is the quality of life assessment by the QLQ-C30 at six months, with three subscores (global health status score,

physical functioning, emotional functioning) being assessed independently. In order to take into account the stepped-wedge design and the specific issues associated with its analysis (clustering, possible temporal effects, variable cluster size, and others), generalised mixed linear models will be used [38]. Since variables to be explained are quantitative (normalised scores), mix linear regression models will be used.

A fixed effect on HRQoL at baseline and random effects on the site, the time, and the time of measurement (before/after the intervention is implemented) will be introduced if data is suitably structured [39]. A directed acyclic graphs (DAG) tool [40] representing causal relationships between variables will be used to identify other potential adjustment factors. A transformation of the global score may be necessary. The multiplicity of tests will be taken into account by adjusting the *p*-value using a family-wise error rate method [41].

3.2.2. Analyses of secondary end-points

For other quality of life items, survival, patient autonomy, anxiety, patient experience, patient and health-care provider satisfaction, and patient institutionalisation, logistic or linear regression models – depending on the distribution of variables – will be used to assess the data, with a similar approach as the primary end-point. By adding a random effect on the patient, this model can take the different follow-up times (3, 6, 9, or 12 months) or the different centres into account. For institutionalisation and unscheduled hospital admissions, frailty models, nested frailty models, or joint nested frailty models will be used depending on the outcome of interest.

The economic evaluation and any analyses of the study costs and outcomes will be carried out according to the intention to treat principle. Both a trial-based economic evaluation and a model-based economic evaluation will be performed. In the trial-based economic evaluation, costs, and consequences of the GERONTE intervention against the standard care will be analysed over the entire trial duration (30 months), while in the model-based economic evaluation, costs and consequences will be instead assessed beyond the trial duration, considering a lifetime perspective for the GERONTE intervention equal to 10 years. In both analyses, a standard discount rate of 3% per year will be applied to both healthcare costs and outcomes [42].

Data collected as part of the ancillary study will be analysed through a realistic approach [43] utilizing the domain of the Consolidated Framework for Implementation Research (CFIR) [44], a well-operationalized framework to assess domains associated with the adoption, implementation, and maintenance of evidence-based interventions.

4. Discussion

The second phase of the GERONTE project will consist of two identical clinical trials (FRONE and TWOBE) that will evaluate the effectiveness of a new care pathway supported by digital health technology for older patients with cancer and multimorbidity. Both trials will assess the effect on quality of life, survival, autonomy, anxiety, unplanned hospitalisations, institutionalisations, and satisfaction with the intervention.

In the clinical trials, the randomisation concerns the timing of the switch of each centre to the intervention arm; each centre will eventually implement the intervention but the order in which the centres switch is determined at random. Randomisation at patient level was not considered feasible, as it is likely that as healthcare professionals are exposed to the intervention, these experiences and some procedures may seep into usual care, thus gradually decreasing the difference between the two arms over time. In the GERONTE trials using a stepped-wedge design, there is a specific moment when a centre switches to the intervention, thus preventing this issue.

A complicating factor is that care as usual is likely to differ between countries and between centres, particularly in geriatric oncology where the level of collaboration between cancer teams and geriatrician is frequently determined by the motivation of individual healthcare professionals. While ideally the GERONTE trials would take place in centres that had not yet introduced any kind of geriatric oncology-related procedures or care to maximize the potential benefit, these centres will be hard to find and also are unlikely to be interested in a geriatric oncology trial that will require a significant change in their clinical practice. Thus, it was decided that centres could participate even if they had already started implementing some of the components of the care pathway, as this reflects current standard care. If we had chosen a study design where randomisation merely allocates centres to the control or the intervention arm, the actual effect of the intervention may be confounded by differences between centres in their current care practices. However, by using a stepped-wedge design, centres become their own comparator and thus variation in current healthcare practice is not an issue [45]. For each centre, the baseline, usual care, will be charted as well as the extent of implementation of the new intervention to provide data on the change in care that resulted from implementing this care pathway.

Additionally, by performing two separate trials in three European countries whose healthcare systems differ in terms of strength of primary care organisation, access to geriatric care, organisation of hospital care, the presence of advance practice nurses, and medical education, the impact of the GERONTE intervention may differ in the two trials. This will provide insight into barriers and facilitators to the implementation of the GERONTE care pathway. This will enable the identification of best practices for better care management and quality of life in older patients with multimorbidity at the European level. Combined with the socio-economic evaluations that will be performed, these data will feed the third phase of the GERONTE project, which consists of developing a roadmap including a detailed business model for implementation of this pathway in other European countries – each with their own healthcare systems - or for other disease clusters. If the trial is successful, it will be an important step forward in improving the care provided to the ever-increasing population of older patients with multimorbidity.

The sample size calculation was carried out on the assumption of a simple (exchangeable) correlation structure. The current standard in stepped-wedge tests is to have a more complex correlation structure, for example two period decay or discrete time decay [46]. With the same assumptions, the power would be 87% and 77%, respectively. In the analysis, several variance-covariance structures of the random effects will be tested. The choice of the best model will be made on statistical criteria (AIC, BIC, AICC). In case of contradictory results, the simplest model will be chosen.

Regarding statistical analysis, a precise statistical analysis plan was drawn up before the start of the trial and a summary is presented in this article. However, stepped-wedge trials are a fairly recent innovation and new developments in the analysis of these designs appear every year. We will continue to keep abreast of the literature to propose the most appropriate method at the time of data analysis, while remaining unaware of the data to avoid potential bias.

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Authors' Contributions

Study concepts: PS HW SR SO MEH LF AS FSG SMP.
Study design: all.
Data acquisition: n/a.
Quality control of data and algorithms: n/a.
Data analysis and interpretation: n/a.
Statistical analyses: LF AS VT MK.

Manuscript preparation: LD MEH CK HW VT.
Manuscript editing: all.
Manuscript review: all.

Declaration of Competing Interest

None.

Availability of Data and Materials

In GERONTE, all of the data associated with scientific publication (journal article, conference contribution, etc.) will be made openly available via the ZENODO GERONTE community (https://zenodo.org/communities/GERONTE/) and linked to the original publication via its digital object identifier (DOI).

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2024.101761.

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