



STREAMLINED GERIATRIC AND ONCOLOGICAL EVALUATION BASED ON
IC TECHNOLOGY
FOR HOLISTIC PATIENT-ORIENTED HEALTHCARE MANAGEMENT
FOR OLDER MULTIMORBID PATIENTS

HORIZON 2020 PROGRAMME – TOPIC H2020-SC1-BHC-24-2020
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D4.4: First study subject approvals package for TWOBE

Lead Beneficiary : 2-KUL

Involved Beneficiaries : 1-UBX 2-KUL 3-DIAK

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History of Changes

Version	Date	Author	Description of change
V1.0	2022-09-29	Pierre Soubeyran [UBX]	First version
V2.0	2023-02-01	Lien Degol [KUL]	Modifications following the expert opinion
V3.0	2023-05-31	Lien Degol [KUL]	Update at M26

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Executive Summary

Deliverable work status

Deliverable	Completion status in %	Deviation	Data complete or to be updated
D4.4 First study subject approvals package for TWOBE	75% at M18 100% at M26	Deviation of content and deviation of timeline (see 'Justification for delay in deliverable submission')	Data complete
Associated Deliverables	D4.4 First study subject approvals package for TWOBE		
Associated Objectives	O4.1 Establish the protocol for two RCT (FRONE in France, TWOBE in both Belgium and the Netherlands) to demonstrate the clinical relevance of GerOnTe		

Description of deliverable

This deliverable is the study approvals package for TWOBE, it will include the final version of the TWOBE trial protocol, the registration number of the clinical trial (clinicaltrials.gov) and the regulatory and/or ethics approvals.

This deliverable is connected to D4.3 First study subject approvals package for FRONE. The research protocol is first developed for clinical trial FRONE, and afterwards adapted to TWOBE considering the Belgian and Dutch regulations.

The deliverable is associated to O4.1 Establish the protocol for two RCT (FRONE in France, TWOBE in both Belgium and the Netherlands) to demonstrate the clinical relevance of GerOnTe.

Attainment of the objectives and explanation of deviations

Attainment of the objectives

The objectives related to this deliverable have not been achieved in full as described in Annexe 1 (Description of the Action Part A) of the Grant Agreement N°945218 yet. This first version of the package (submitted at M18) delivers the latest versions of the TWOBE trial protocol, the first version submitted to Belgian national authorities and the second version submitted to the Dutch national authorities. The delay in the original submission of this deliverable will be explained in the section below.

This update at M26 delivers the ethical and regulatory approvals for TWOBE and the registration of the trial at clinicaltrials.gov.

Explanation of deviations

For D4.1, which consequently also affects D4.4, we stated in the Grant Agreement that the number of patients recruited per clinical trial would be 634 and per centre would be 79-80 patients during 18 months accrual in order to evaluate the impact of the GerOnTe intervention on Quality of Life at 1 year. It was initially planned that the study duration would be 1 year for all included patients, and that Quality of Life would be evaluated for each patient at 3, 6 and 12 months, taking the 12 months Quality of Life as primary endpoint, and 3 and 6 months Quality of Life as secondary endpoints.

During the development of the research protocol, the GerOnTe Trial Development Team (TDT) had intense discussions on the optimal timing of Quality of Life evaluation as primary endpoint. We decided to maintain the 1-year follow-up for all patients, and keep the 3, 6 and 12 months Quality of Life evaluation, but changed the primary endpoint from 12 months to 6 months.

The main reason for this change in primary endpoint was the concern about an excessive drop-out rate if all patients had to reach the 12 months' time point to complete the study. At KU Leuven (KUL), a recent, unpublished trial was performed with a geriatric intervention including a similar population. The primary endpoint for that trial was Quality of Life at 6 months.

First analyses (that became available in 2022) showed that dropout range was around 20% at 6 months in this population. These numbers were not available when the initial grant proposal was written in 2018. The GerOnTe Trial Steering Committee (TSC) decided to change the primary endpoint from 1 year to 6 months because there were concerns that the dropout rate would be too high at 12 months. It was also decided to increase the allowed dropout rate at 6 months from 10% to 20%.

The Trial Steering Committee (TSC) evaluated that it was not needed to put the expected dropout rate for GerOnTe higher than 20% since the GerOnTe population (breast, lung, colorectal, prostate cancer, including many patients treated with local therapy alone) has a better 'oncological prognosis' than the KU Leuven trial that included all tumor types, and only allowed patients starting systemic therapy. A new sample size calculation was performed based on these assumptions. Based on this calculation, the number of patients to be recruited was changed from 634 to 720 per clinical trial. Per clinical site, 90 patients will be recruited during the 18 months of inclusion. This change would only require a minor increase in accrual rate per site (10 patients per 2 months instead of 8 patients per 2 months), and this was assessed as easily feasible by all sites (given the broad inclusion criteria that were established). In addition, this change does not have any impact on the study accrual period or the 12 months follow-up per patient that was planned anyhow.

Justification for delay in deliverable submission

A delay in D4.4 as scheduled in Annexe 1 (Description of the Action Part A) of the Grant Agreement N°945218 has an impact on the start date of the clinical trials (further WP4 tasks and deliverables) and all tasks and deliverables of other work packages related to the clinical trials. The start date of the clinical trials will be delayed. There are several reasons for this delay :

1. Clinical trial protocol finalisation:
 - a. The eligibility criteria were finalised in January 2022. It took some time before there was a consensus on eligibility criteria. Several cancer specialists from different areas of expertise outside the Trial Development Team were contacted to provide input into the tumor specific inclusion criteria (see meeting minutes in-exclusion criteria in

annex). This input from different perspectives was very valuable in creating a good balance between accessibility of the clinical trials, but also reaching patients with cancer therapy that has sufficient impact on daily life.

- b. The study design of the GerOnTe study was discussed several times in the Trial Development Team. The stepped wedge design is a design well suited for the GerOnTe study, but has some conditions that need to be respected. The methodological and statistical team clarified possible deviations from the study design and stated what adjustments should be made to maintain good statistical power (see meeting minutes TDT 18/01/2022).
- c. A number of activities in other work packages of the investigation needed to be completed to inform the clinical trial protocol (WP1, WP3, WP5) e.g. the participant flow, the development of the Holis™ GV digital tool and the information to be included in the Holis Dashboard, the use of automated or non-automated tools, the way to collect the information from patients and caregivers, the questionnaires that will be used, etc. WP3 and WP5 provided the list of questions and characteristics of the involved people related to the health sociological study and assessment in June 2022.
- d. The results from small scale pilot studies were initially slated to inform the clinical trial protocol, and the start of these pilot studies were delayed until Q1 2022. The one-month delay regarding the organisation of the small-scale pilot studies was caused by the small delays related to the development of the application, which delayed the envisioned timeline by one month (planned for M12 as described in Annex 1 (Description of the Action Part A) of the Grant Agreement, but delivered in M13). Also access to the hospital servers and implementation of the automated dashboard was a concern for the feasibility of the trials. The decision to use a non-automatic dashboard was taken. As said in D6.2, due to added demands from GerOnTe project partners the Holis™ GV platform with all its modules originally planned to be ready by the end of December (M9) was delayed and finalized in February. Hence, pilots had to take place from the beginning of March (M12) to mid-April (M13). The respective deviation did not influence the achievement of the project's objectives. Launching of the small-scale pilots in three countries required a period of preparation from all participating partners. As there were three different approaches to conduct the pilots, MyPL started to work with KUL, ESE, UBx, DIAK in February-March 2022 in order to make sure that they have all necessary elements to start the pilots in due time. The small-scale pilots lasted one month until mid-April 2022, whereas the results were made available at the end of April with the submission of the Deliverable 6.3. In addition, a consortium meeting was organised on the 20th of May, 2022, to discuss the small-scale pilots results and the problems identified.
- e. The clinical trial development has to take into account regulatory aspects of three different countries for clinical trials, i.e. the issue of qualification is made more complex due to the new medical device regulation (MDR, May 2021), which may apply in some countries but not in others. Querying, collecting and discussing/comparing national and hospital-specific requirements has also caused more delays than expected.
- f. Establishing which category the trial should be submitted to in Belgium and the Netherlands took longer than expected. Only afterward could be determined what documents were needed and has to be developed for national submissions in each country. Since the GerOnTe study in Belgium and the Netherlands had to be submitted

according to the Medical Device Regulation (MDR), a lot of documents also had to be developed regarding the medical device. This required increased input from other work packages, including WP2. Some documents concerning the Holis Dashboard and Holis Patient App were available late as the development of the Holis™ GV digital tool was not yet finished (see meeting minutes TDTs).

2. Recruitment project manager UBx (EUCLID):

- a. It proved difficult to find a good candidate for the recruitment of a project manager at UBx (EUCLID), who could fully devote themselves to the GerOnTe trials. No other study staff at IB or EUCLID could take over the full activities. A transitory solution was for a senior project manager at IB to devote part of her time to the project but this could only be limited in time (1day/week) and duration (October to December 2021). Moreover, the COVID-19 pandemic context added complexity and delays to the process of recruitment and start of activities of the Trial Development Team (TDT).

The job posting for the position of clinical trial project manager was advertised on the following websites:

- The University's of Bordeaux's website
- The APEC website ('Association pour l'emploi des cadres') ref: 166888395W
- Place de l'Emploi Public référence 2021-654544
- LEEM (Les entreprises du médicament) reference CDP-Ger-01
- Pôle Emploi ref : 119GQYW
- Euraxess website
- ISPED website ('L'Institut de Santé Publique, d'Epidémiologie et de Développement')

The position was also advertised on the project's social media accounts, shared by several UBx staff on their own pages. It was also shared by the project's scientific coordinator to various networks he is a part of. Proof of the posting is provided in the annexes of this report, under WP4's annexes.

The delay in recruiting a clinical trial project manager is due to a general shortage of qualified candidates for the different positions in clinical research. Issues that can be knotted are the lack of academic training specific to clinical research, the unattractiveness of academic positions/offers compared to industry/CRO offers in terms of salary, and type of contract (permanent/long-term versus reconductible every year for a maximum of 4 years).

International multicentre clinical trials require special skills and a proven expertise in management of previous trials, this specific position cannot be filled by a junior in the field, let alone someone who has never managed a trial. We mainly had candidates who had been CRAs for a year or two and had never been trial manager or candidates who did not fit the profile at all including no experience in clinical research at all.

All and all, from 8th July 2021 to 28th September 2021, we only received 8 CVs, of which only one fit the exact profile and was hired. All the other candidates had little to no experience or even theoretical in clinical research. The candidate was interviewed first on 1st October and second on 8th October 2021. We notified her that we were offering her the position on 14 October after having received the salary

information from University of Bordeaux. She accepted the offer on 21 October after a couple of exchanges re salary. Her start date was the 15th of January 2022.

1. Introduction

1.1. GERONTE and its objectives

GERONTE is a 5-year research and innovation project (April 2021 to Mars 2026) funded by the European Union within the framework of the H2020 Research and Innovation programme, in response to the health societal challenge topic SC1-BHC-24-2020 “Healthcare interventions for the management of the elderly multimorbid patient”. The overall aim of GERONTE is to improve quality of life - defined as well-being on three levels: global health status, physical functioning and social functioning- for older multimorbid patients, while reducing overall costs of care. To this end, GERONTE will co-design, test, and prepare for deployment an innovative cost-effective patient-centred holistic health management system, hereafter referred to as the GERONTE intervention. GERONTE intervention will rely on an ICT based application for real-time collection and integration of standardised clinical and home patient-reported data. GERONTE intervention will be demonstrated in the context of care of multimorbid patients having cancer as a dominant morbidity, and be adaptable to any other combination of morbidities.

Objectives

01: INFORMATION gather the stakeholders and data needed for patient-centred and multi-actor complex decision-making process and management

02: TOOLS develop ICT tools for the GERONTE intervention to be implemented

03: METHODS develop socio-economic methods for evaluating the impacts of the implementation of the GERONTE intervention

04: DEMONSTRATION demonstrate in 16 study sites from three EU countries the feasibility and effectiveness of the GERONTE intervention

05: REPLICATION develop recommendations for the replication of GERONTE best practices in all European health systems

06: ENGAGEMENT engage all stakeholders by co-designing the GERONTE intervention

1.2. Rationale

Deliverable D4.4 is part of work package 4 which supports GerOnTe objective 2. Develop the Holis™ GV tool for the GerOnTe model to be implemented and objective 4. Demonstrate in 16 study sites from three EU countries the feasibility and effectiveness of the GerOnTe model.

The objective of WP4 is to perform two clinical trials, i.e. FRONE in France and TWOBE in Belgium and the Netherlands, in accordance with ethical and regulatory requirements. The goal is to provide a Proof of Concept of the GerOnTe model in three distinct European countries, and (i) to provide data on how the GerOnTe intervention fits into different health organisation systems, and (ii) to quantify the effectiveness and efficiency of GerOnTe system. All details are provided in the essential annexe for clinical studies.

2. Clinical trial protocol

The latest version of the TWOBE clinical trial protocol submitted to Belgian authorities can be found in Annexe 1. The latest version of the TWOBE clinical trial protocol submitted to Dutch authorities can be found in Annexe 2.

3. Regulatory and ethical approval Belgium

The written regulatory and ethical approval of Federal Agency for Medicines and Health Products (FAMHP), the national competent authority in Belgium, for TWOBE can be found in Annexe 3.

4. Regulatory and ethical approval the Netherlands

The written regulatory and ethical approval of Medical research Ethics Committees United (MEC-U), the national competent authority in the Netherlands, for TWOBE can be found in Annexe 4.

5. Trial registration

The clinical trial GerOnTe TWOBE is registered on June 21, 2022 in ClinicalTrials.gov with registration number NCT05423808.

6. Conclusion

This deliverable is the study approvals package for TWOBE, this first version of the package delivers the latest versions of the TWOBE trial protocol in annexes, the first annex is the version of the protocol submitted to Belgian authorities and the second annexe is the protocol submitted to the Dutch authorities. This update includes the Belgian and Dutch regulatory and ethical approval for TWOBE as well as the registration of the trial at clinicaltrials.gov.

7. Annexes

7.1. Annex 1: TWOBE protocol as submitted to Belgian authorities

STREAMLINED GERIATRIC AND ONCOLOGICAL EVALUATION BASED ON IC TECHNOLOGY FOR HOLISTIC PATIENT-ORIENTED HEALTHCARE MANAGEMENT FOR OLDER MULTIMORBID PATIENTS

TWOBE Protocol

Medical device investigation under the European Regulation 2017/745 on Medical Devices (MDR)
Article 82

Version n°0.2 25/09/2022

This project has obtained funding from the Horizon 2020 Program - Topic H2020-SC1-BHC-24-2020

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APPROVAL AND SIGNATURES OF PROTOCOL

Title of protocol : Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients. TWOBE study.

Ethics Committee Belgium	Name: XXXXXXX	Initial approval date	
		Reference	
Ethics Committee the Netherlands	Name: XXXXXXX	Initial approval date	
		Reference	

Name and responsibility	Address	Date	Signature
Coordinating Investigator			

For Belgian sites: I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of December 22nd 2020 on medical devices, the Regulation (EU) 2017/745 of 5 April 2017 on medical devices, the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other applicable legal and regulatory requirements and Standard Operating Procedures (SOPs), and any subsequent amendments of the foregoing.

For Dutch sites: I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the Good Clinical Practice (decision of 24 November 2006), the Dutch law regarding medical research

involving human subjects (WMO), the EU General Data Protection Regulation 2016/679 (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (AVG).

I assume my responsibilities as referent investigator including:

- Collection of informed consent, dated and signed by participants before any selection procedure in the protocol,
- Validation of case report forms, completed for each participant included in the study,
- Direct access to source documents for verification by the clinical research assistant (CRA) commissioned by the sponsor,
- Archiving of critical documents of the study for a 25 year-period.

Name and address of the investigating centre:

Name of the Principal Investigator :

Date : |_|_| |_|_| |_|_|_|_|

Signature :

SYNOPSIS

Title of the study	Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients. TWOBE study.
Abbreviation of the trial	GerOnTe – TWOBE
Sponsor Identification	KU Leuven/UZ Leuven, Leuven, Belgium
Coordinating Investigator	Prof. Hans WILDIERS Department of General Medical Oncology, UZ Leuven, Belgium
National Principal Investigator for Belgium	Prof. Hans WILDIERS Department of General Medical Oncology, UZ Leuven, Belgium
National Principal Investigator for the Netherlands	Dr. Marije HAMAKER Department of Geriatrics, Diaconessenhuis, the Netherlands
Number of investigational sites planned	8 centres : <ul style="list-style-type: none"> - Belgium : 4 centres - The Netherlands : 4 centres
Number of participants	720 participants
Duration of the study	Planned enrollment period: 18 months Follow-up period: 12 months Study period: 36 months
Study rationale	<p>The heterogeneity of older patients in terms of health status, physical functioning and intrinsic capacity makes their evaluation complex. In those aged 65 to 84, the proportion of patients with multimorbidity is as high as 65% and rises to 81% in those aged 85 or older. Currently, in Europe, acute-hospital care is mainly single-disease oriented. As a result, coexisting morbidities are often under-evaluated and under-managed, leading to inappropriate drug prescriptions, avoidable hospital admissions, delays in treatment and ultimately to suboptimal care and unnecessary cost overruns. Moreover, because of different health organisations, management of older multimorbid patients varies from one country to the other while we know that the structure of health system organisation has a strong impact on patients' health status. Finally, none is currently structured to absorb the demographic increase of older patients.</p> <p>People with multimorbidity have reduced quality of life and impaired health outcomes and experience a significant impact of disease burden and an increased risk of death that current disease-centred management, which impacts patients' quality of life and quality of care, cannot manage.</p> <p>Disease-centred approach is not appropriate to manage these patients. Change to a patient-centred approach will simplify care pathways, secure management and treatment decision making and decrease healthcare costs. It will be a real breakthrough for daily practice with multiple impacts that must be quantified.</p> <p>The clinical model behind GerOnTe is to regroup all health professionals taking care of a multimorbid patient, into a common care coordination pathway: the Health Professional Consortium (HPC). The HPC will (i) centralise the decisions, aligning them to the patient's priorities, (ii) be assisted by an advanced practice nurse (APN) as case manager, and (iii) be facilitated by HolisTM GV data exchange, personalised</p>

	<p>for each patient. Patients will be stratified in order to determine their dominant disease, thus the appropriate HPC. Patient-centred health management by the HPC with availability of real time, hospital- and patient-based data will foster timely decision enabling avoidance of unnecessary procedures and treatments leading to reduction in number of ineffective treatments, complications and unscheduled hospitalisations, concerted treatments of multimorbidities, and to more patients staying at home thanks to self-management related reduction of dependence.</p> <p>The whole approach will be co-designed with patients, informal care givers and health professionals. Cancer is an excellent model to develop this approach in multimorbid patients because it is frequent and commonly associated with other morbidities in older patients but also because of its major impact on patients' general status and coexistent diseases. Cancer already benefits from a multidisciplinary management model that GerOnTe will enhance, strengthening exchange of holistic data, role of primary care and case management. GerOnTe will also provide new country-specific guidelines and best practices for implementation across Europe and for improved management of older multimorbid patients including improved quality of life and independent living at decreased costs.</p> <p>The GerOnTe project consists of two identical trials in two different European geographical areas, FRONE in France and TWOBE in Belgium and the Netherlands. The goal of two identical trials is to take into account the role of health care contexts in the implementation, effectiveness and efficiency of the GerOnTe intervention.</p>
Medical conditions	Multimorbid patient with new or progressive cancer (breast, lung, colorectal, prostate)
Objectives	<p>PRIMARY OBJECTIVE: to evaluate the effectiveness of the GerOnTe, ICT-based, integrated care pathway to improve patient 6-month quality of life, in Belgium and the Netherlands.</p> <p>SECONDARY OBJECTIVES</p> <ul style="list-style-type: none"> • Evaluate the effectiveness of the GerOnTe patient-centred system to: <ul style="list-style-type: none"> ○ Improve quality of life at 3, 9 and 12 months, ○ Improve patient survival and progression-free survival at 12 months, ○ Improve patient autonomy at 3, 6, 9 and 12 months, ○ Reduce patient anxiety at 3, 6, 9 and 12 months, ○ Reduce patient unscheduled hospitalisations and patient institutionalisations at 6 and 12 months, • Assess the cost-utility and cost-effectiveness of the GerOnTe intervention versus standard of care up to 1-year post-inclusion (3, 6, 9 and 12 months after inclusion), • Evaluate caregiver burden in health, psychological well-being, finances, social life and relationship with patient at 3, 6, 9 and 12 months, • Evaluate patient-reported overall experience of the GerOnTe intervention at 6 and 12 months, • Evaluate patient and health care professionals reported overall satisfaction and acceptability of the GerOnTe intervention at 6 and 12 months, • Analyze the implementation and use of the GerOnTe patient-centred intervention by patients and health care professionals
Study design	Study design is a stepped wedge randomized controlled trial. Clusters will be participating hospitals, comprising eight investigating sites in total. Patients

	<p>included at each “step” are different individuals. The first “step” is a reference measurement where none of the clusters will implement the intervention. The investigating sites will be randomly drawn to determine the order in which they will implement the intervention, by “steps” of two months.</p> <p>Each centre engaged to participate needs to participate till the end of the trial. A centre commitment to participate will be requested before each centre involvement to avoid centre withdrawal after the start of the trial.</p>
Inclusion criteria	<p><u>General inclusion criteria</u></p> <ol style="list-style-type: none"> 1. Age \geq 70 years old. 2. New or progressive cancer (breast, lung, colorectal, prostate) fulfilling the tumour specific criteria. 3. Estimated life expectancy greater than 6 months. 4. At least one moderate/severe multimorbidity inclusion criteria other than current cancer (see separate list under 5.3). 5. Patients must be willing and able to comply with study procedures. 6. Voluntarily signed and dated written informed consents prior to any study specific procedure. 7. QLQ-C30 Quality of Life Questionnaire fully completed at baseline, before inclusion. <p><u>Tumour specific inclusion criteria</u></p> <ol style="list-style-type: none"> 8. Specific inclusion criteria for breast cancer: <ol style="list-style-type: none"> 8.1. <u>Non-metastatic breast cancer (M0)</u>: <ul style="list-style-type: none"> • No prior treatment for the current breast cancer. • All 3 criteria required: <ul style="list-style-type: none"> ○ Clinical staging: cT2-3-4 Nany, or cTany N1-2-3, ○ The cancer specialist considers* surgery, ○ The cancer specialist considers* radiotherapy and/or chemotherapy. 8.2. <u>Metastatic breast cancer (M1)</u>: Both criteria required: <ul style="list-style-type: none"> • The cancer specialist considers* chemotherapy or PARP-inhibitors or mTOR-inhibitors / PIK3CA inhibitors; Previous endocrine therapy +/- CDK4/6 inhibitors is allowed, • The patient received maximum 1 prior line of chemotherapy for metastatic disease. <p><i>*‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.</i></p> 9. Specific inclusion criteria for colorectal cancer: <ol style="list-style-type: none"> 9.1. <u>Non-metastatic colorectal cancer (M0)</u>: <ul style="list-style-type: none"> • No prior therapy for the current tumour in the recruiting hospital. • At least one of the 3 criteria required: <ul style="list-style-type: none"> ○ The cancer specialist considers* surgery, ○ The cancer specialist considers* radiotherapy, ○ The cancer specialist considers* chemotherapy. 9.2. <u>Metastatic colorectal cancer (M1)</u>: <ul style="list-style-type: none"> • The cancer specialist considers* first line systemic therapy and/or radiotherapy (+/- surgery). No previous chemotherapy allowed except

adjuvant/perioperative chemotherapy stopped for more than 12 months.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

10. Specific inclusion criteria for **lung cancer**:

10.1. Non-metastatic lung cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery (patients considered for treatment with percutaneous thermoablation alone are not eligible),
 - The cancer specialist considers* radiotherapy (except SBRT),
 - The cancer specialist considers* systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

10.2. Metastatic lung cancer (M1):

- The cancer specialist considers* first or second line systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

11. Specific inclusion criteria for **prostate cancer**:

11.1. Non-metastatic prostate cancer (M0): one of the following:

- First diagnosis M0 prostate cancer (no therapy received yet for prostate cancer): at least one of the 2 criteria required:
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* hormone therapy (ADT +/- combination Abiraterone and Prednisone).
- Salvage treatment M0 prostate cancer (received prior surgery at least 6 months before):
 - The cancer specialist considers* radiotherapy (+/- ADT)
- Non-metastatic castration resistant prostate cancer:
 - The cancer specialist considers* treatment intensification (ADT + Enzalutamide or Apalutamide or Darolutamide).

11.2. Metastatic prostate cancer (M1):

- The cancer specialist considers* treatment with Abiraterone or Enzalutamide or Apalutamide or Docetaxel or Cabazitaxel or PARP-inhibitors or Lutetium PSMA.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

Exclusion criteria	<ol style="list-style-type: none"> 1. Mental illness/cognitive impairment that limits ability to provide consent or complete trial procedures. 2. Participating to an interventional clinical trial with a non-registered anticancer drug or to another geriatric intervention trial. 3. Patients and caregivers are unable or unwilling to use ICT-devices (tablet, computer, smartphone) or the Internet according to protocol. 4. Patient already included in this study.
Control arm	Patients included in the control arm will be managed according to the standard of care.
Intervention schedule	<p>The intervention will include the following components:</p> <ul style="list-style-type: none"> • A health professional consortium (HPC) for each patient, which will work together to make recommendations regarding oncologic treatment and non-oncologic interventions, at baseline and in the course of treatment. This will be in addition to the usual multidisciplinary tumour board (MTB) which will provide oncologic treatment recommendations based on the usual oncologic work-up. • An advance practice nurse (APN) as case-manager, who will be the primary contact person for the patient during the oncologic treatment and subsequent follow-up • A baseline patient evaluation consisting of a comprehensive geriatric assessment by a geriatrician or APN, which will focus on general health status, comorbidities and intrinsic capacity. Baseline documentation of patient preferences and priorities will be done by the APN. • A health care professional dashboard called Holis Dashboard, which 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 the standard consensus dataset. Dashboard data will be made available selectively to all health care professionals of the HPC. • A patient application called Holis Patient Application, which will allow for monitoring of symptoms and signs of destabilised comorbidity or functional decline during and after treatment, with additional self-management library with recommendations for how the patient can deal with issues or for contacting their health care providers in case of symptoms requiring urgent intervention. • Additional data that will be collected every 3 months are quality of life questionnaires (EORTC QLQ-C30/QLQ-ELD14/EQ-5D-5L), autonomy questionnaire (Katz ADL), anxiety/depression questionnaire (HADS), patient-related outcomes questionnaire (perceived benefit, treatment objectives, tool satisfaction) and possible revision of patient's treatment objectives.
Endpoints	<p>PRIMARY ENDPOINT</p> <p>Quality of life assessed by the EORTC QLQ-C30 questionnaire at 6 months after GerOnTe inclusion using 3 derived scores of the QLQ-C30 questionnaire:</p> <ul style="list-style-type: none"> • Normalized global health status score • Normalized score of the physical functioning scale • Normalized score of the emotional functioning scale <p>SECONDARY ENDPOINTS</p> <ol style="list-style-type: none"> 1. Quality of life <ul style="list-style-type: none"> • The 3 normalized QLQ-C30 scores at baseline 3, 9 and 12 months

	<ul style="list-style-type: none"> • Normalized scores of QLQ-C30 scales/items (role functioning scale, cognitive functioning scale, social functioning scale, fatigue scale, nausea scale, pain scale, dyspnea item, insomnia item, appetite loss item, constipation item, diarrhea item and financial difficulties item) at baseline, 3, 6, 9 and 12 months. • Scores of QLQ-ELD14 scales/items (mobility scale, worries about others scale, future worries scale, maintaining purpose scale, burden of illness scale, joint stiffness item, family support item) at baseline, 3, 6, 9 and 12 months <ol style="list-style-type: none"> 2. Survival: Overall survival at 12 months and progression-free survival (the time from study treatment initiation to the first occurrence of disease progression or death, whichever occurs first). 3. Patient autonomy, frailty and weight evolution <ul style="list-style-type: none"> • Dependence score of the Activities of Daily Living scale (Katz ADL) at baseline, 3, 6, 9 and 12 months, • Proportion of patients living at home at 6 and 12 months, • Number of completed chair stands in 30 seconds (Chair stand test) at baseline, 3, 6, 9 and 12 months, • Score of the Clinical Frailty Scale at baseline, 3, 6, 9 and 12 months, • Grade of performance status, measured by ECOG-PS at baseline, 3, 6, 9 and 12 months, • Weight at baseline, 3, 6, 9 and 12 months. 4. Patient anxiety: Score of Hospital Anxiety and Depression Scale (HADS) at baseline, 3, 6, 9 and 12 months. 5. Proportion of patient institutionalized and number of unscheduled hospitalisations per participants at 6 and 12 months. 6. Cost per life years gained (CEA, derived from survival/progression-free survival), cost per QALY gained (CUA, using utility assessed through normalized scores of EQ-5D-5L questionnaire collected at baseline, at 3, 6, 9 and 12 months after inclusion) and incremental cost-effectiveness ratios (ICERs) obtained by a cost-utility and a cost-effectiveness analysis. 7. Caregiver burden in health, psychological well-being, finances, social life and relationship with patient, using the Zarit Burden Interview at baseline, 3, 6, 9 and 12 months 8. Patient reported overall experience of person-centred coordinated care measured through the Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) at 6 and 12 months. 9. Patient, physician and health-care-professionals-reported overall satisfaction with the IC technology of the GerOnTe system: Score derived from the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps using the patient version for patient satisfaction and the provider version for physician and health care professional at 6 and 12 months after inclusion. 10. GerOnTe patient-centred system implementation and usage evaluated at 6 months (use of the Holis Patient App measures, for instance: number and frequency of connections to the app by patients; number of web-based meetings with APN by site)
Statistical considerations	<p><u>Hypothesis and number of participants needed</u></p> <p>Sample size calculation was drawn to detect a mean difference of 10 points or more (on a score from 0 to 100) (Osoba 1998), should the intervention be effective, for at least one of the three targeted health-related quality of life (HRQoL) scores (common standard deviation of 20 points).</p> <p>With a 1.6% two-sided type I error (accounting for the 3 comparisons), a statistical</p>

power of 90%, and accounting for a possible 20% dropouts, the total minimum number of patients to be included is 278. 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 corresponding to 10 patients on average per step and per centre.

Definition of study population

Main analysis will be performed among the intention-to-treat population: all patients will be included in the analysis in the group in which they were initially randomised and all their data will be used.

A per protocol population can be used in secondary analysis including only patients who are strictly compliant with the procedure (lost-of-follow-up will be, in particular, excluded).

Statistical analysis

Descriptive analysis will always be presented overall and by treatment group.

The primary endpoint is the Quality of Life assessed by the EORTC QLQ-C30 (version 3.0) questionnaire at 6 months after GerOnTe implementation. It has 3 sub-scores that will be analyzed independently, with alpha risk adjustment.

In order to take into account, the stepped wedge study design and its specificities (possible temporal effect, variable cluster size, presence of clusters), generalized mixed linear models will be used (Husset & Hughes 2007). Since the variables to be explained are quantitative (normalized scores), mixed linear regression models will be used. Random effects on the site, the time and the time of measurement (before/after the intervention is implemented) will be introduced where possible. The multiplicity of tests will be taken into account by adjusting the p-value using a Family-wise error rate method (Burman Stat Med 2009).

Secondary endpoints will be analyzed using the same strategy as the primary endpoints. Longitudinal data (repeated measure across the 4 follow-up times) can be analyzed adding a random effect on the patient.

Concerning the cost-utility and cost-effectiveness analysis:

The economic evaluation will be conducted from a societal perspective for primary analysis (which accounts both the costs in the public payer perspective and other direct and indirect costs relevant for different stakeholders, including patients). A secondary analysis will additionally be conducted from the payer perspective only, with the aim to estimate the budgetary impact on public finances. In this case, only the resource used within the hospital setting will be considered.

Costs will be calculated considering resource use at patient level and unit costs of each product/service used in the care pathway. 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 available sources. A map of available patient-level RWD (Real World Data) will be created to generate real-world evidence. Time spent will be measured by microcosting (through interviews and questionnaires) and will inform the economic analysis.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of Daily Living scale
ADT	Androgen Deprivation Therapy
APN	Advanced Practice Nurse
ARS	Regional Health Agency
CEA	Cost per life years gained
CGA	Comprehensive Geriatric Assessment
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Assistant
CRF	Case Report Form
CUA	Cost per QALY gained
CVA	Cerebrovascular Accident
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
DQF	Data Query Forms
EC	Ethics Committee
ECOG	Eastern Collaborative Oncology Group
EHR	Electronic Health Report
EMR	Electronic Medical Record
EORTC	European Organisation for Research and Treatment of Cancer
FAMHP	Federal agency for Medicines and Health Products
FG	Focus Groups
FNCLCC	Federation of Anti-Cancer Centres
GCP	Good Clinical Practice
GDPR	General Data Protection regulation
GP	General Practitioner
GV	Geriatric Version
HADS	Hospital Anxiety and Depression Scale
HPC	Health Professionals Consortium
HRQoL	Health Related Quality of Life

ICER	Incremental Cost-Effectiveness Ratio
ICT	Information Communication Technology
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention To Treat
LYG	Life Years Gained
MAUQ	mHealth App Usability Questionnaire
MDT	Multi-disciplinary Team
MTB	Multidisciplinary Tumour Board
NOAC	Novel Oral Anticoagulant
P3CEQ	Person-Centred Coordinated Care Experience Questionnaire
PFS	Progression-Free Survival
PROMs	Patient-Reported Outcome Measures
PS	Performance Status
QALY	Quality Adjusted Life Year
QKPI	Quality Key Performance Indicators
QLQ-C30	Quality of Life Questionnaire – Core 30 items
QLQ-ELD14	Quality of Life Questionnaire – Elderly Cancer Patients 14 items
RWD	Real World Data
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SNDS	National Health Data System
SOP	Standard Operating Procedure
TCO	Total Cost of Ownership
TDABC	Time-Driven Activity-Based Costing
TSC	Trial Steering Committee
ZBI	Zarit Burden Interview

1. CONCEPT AND RATIONALE OF THE TRIAL

1.1. MANAGEMENT OF MULTIMORBID PATIENTS

The heterogeneity of older patients in terms of health status, physical functioning and intrinsic capacity makes their evaluation complex. In those aged 65 to 84 years, the proportion of patients with multimorbidity is as high as 65% and rises to 81% in those aged 85 or older (Barnett Lancet 2012). The most prevalent morbidities in patients older than 65 are arthritis (57%), hypertension (55%), pulmonary disease (38%), diabetes (17%), cancer (17%), and osteoporosis (16%) (Vogelli J Gen Int Med 2007). Cardiovascular diseases are among the most frequent and the most lethal morbidities in older patients, followed by chronic obstructive pulmonary disease, diabetes, and cancer (Menotti J Clin Epidemiol 2001). Currently, in Europe, acute-hospital care is mainly single-disease oriented (with the exception of geriatricians who perform holistic evaluation and management of patients) (Rijken Health Policy 2018). As a result, coexisting morbidities are often under-evaluated and under-managed, leading to inappropriate drug prescriptions, avoidable hospital admissions (Leendertse Arch Int Med 2008), delays in treatment and ultimately to suboptimal care and unnecessary cost overruns (Ernst J Am Pharm Assoc 2001). Moreover, because of different health organisations, management of older multimorbid patients varies from one country to the other (Kringos Br J Gen Pract 2013) while we know that the structure of health system organisation has a strong impact on patients' health status (Hansen Health Affairs 2015). Finally, current health systems are not structured to absorb the demographic increase of older patients.

People with multimorbidity have reduced quality of life and impaired health outcomes (Salisbury Lancet 2012) and experience a significant impact of disease burden (Rose Qual Life Res 2018; Bayliss Health Qual Life Outcomes 2005) and an increased risk of death (Pereira-Nunez Arch Gerontol Geriatr 2016) that current disease-centred management, which impacts patients' quality of life and quality of care, cannot manage. Without appropriate coordination of care, despite attention and good will of health professionals, because of their intrinsic medical complexity, multimorbid patients may experience multiple problems including interaction between medications or adverse consequences of expected and unexpected events on other morbidities, among other causes. These events will often lead to unscheduled events or hospitalisations, thus impairing quality of life, and even to death in some cases. This is why there is an imperative to develop solutions to effectively manage this complexity.

The current situation should be addressed at a European level and needs benchmarking practices as well as the development of shared, automated and cost-effective solutions for better global implementation. GerOnTe builds on the findings of past EU projects (PHAMEU, SIMPHS, ICARE4EU, JA-CHRODIS and SELFIE) to develop appropriate solutions for the management of patients and to facilitate availability of data to health professionals as well as patients and their informal caregivers, in order to improve care of multimorbid and vulnerable patients (Berntsen J Med Internet Res 2019).

The effective management of patients with multiple morbidities is a key task for healthcare systems, and accounts for a significant part of total healthcare expenditure (Picco BMC Health Serv Res 2016; König BMC Health Serv Res 2013) with wide variability in terms of complexity. Indeed, each multimorbid patient combines different morbidities and medications with a specific medico-social background, leading to multiple possibilities of interactions, which should be understood to prevent unexpected consequences.

The best solution to consider this context is to move towards patient-centred management. Achieving this effectively, and affordably, will require an organisation shift from disease-centred care delivery to patient-centred integrated care delivery. Organisation of care, simultaneous availability of health professionals and resistance to change in organization and work habits will be key issues for which we will need to develop strong arguments based on facts i.e. data from clinical trials with a large set of endpoints directed towards end users and health authorities. It is therefore of crucial importance to develop models based on Total Cost of Ownership (TCO), which will enable organisations to understand cost impacts over time. To avoid

unnecessary interventions, the treatment decision-making process should involve all types of health professionals concerned, and present to all of them concomitantly exhaustive and personalised relevant data for each patient. Above all, the patient's own perception and opinion, and that of their informal caregivers, need to be taken into account during the whole care process. To this end, it is necessary to develop specific social and economic Quality Key Performance Indicators (QKPIs), in order to evaluate the quality of care for people with multimorbidity.

The choice to start in the context of care of multimorbid patients having cancer as a dominant morbidity is motivated by the fact that:

- cancer frequency increases sharply with age for most cancer types and is thus common in older adults, affect 45 to 55% of patients older than 70 (<https://www.cancerresearchuk.org/health-professional/cancerstatistics/incidence/age#heading-Zero>; Defossez Francim 2019);
- cancer and its aggressive treatments have a strong impact on patients' general status, on other co-occurring diseases, and on their treatments;
- at EU-level, a multidisciplinary approach is standard practice for cancer management, minimising the step-change required for real-life validation of GerOnTe during the lifetime of the project;
- once validated, this model will be applicable to any other combination of morbidities with or without cancer, giving to the concept a major potential of generalisability for the older population.

1.2. THE GERONTE CARE SYSTEM

For care in cancer patients, recent data show that real-time information about events during follow-up is useful and that web-based prospective weekly collection of symptoms improves survival (Denis J Natl Cancer Inst 2017, Basch JAMA 2017) and quality of life (Basch J Clin Oncol 2016). Cancer is frequently associated with other morbidities, particularly depression and anxiety, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, and pain, especially in socioeconomic deprived populations (Barnett The Lancet 2012). Multimorbidity is a major cause of reduced survival in all cancer types. Long-term vulnerability and loss of intrinsic capacity are common in older patients, particularly when they develop cancer, which increases risks through the disease itself and its treatment. Cancer is thus an excellent model to validate optimisation of multimorbid patient management pathways because of (i) its strong impact on the patient's general well-being and on other coexistent diseases, and (ii) the potential consequences of its aggressive treatments on other morbidities and their management. GerOnTe will build upon existing multidisciplinary in cancer management (cancer specialists including surgeons, radiation and medical oncologists, as well as geriatricians, radiologists, pathologists, general practitioners, organ specialists, supportive care specialists, nurses, physiotherapists, dieticians, and occupational therapists), bringing a novel use of case management and a strengthened role of primary care thanks to GerOnTe care pathway.

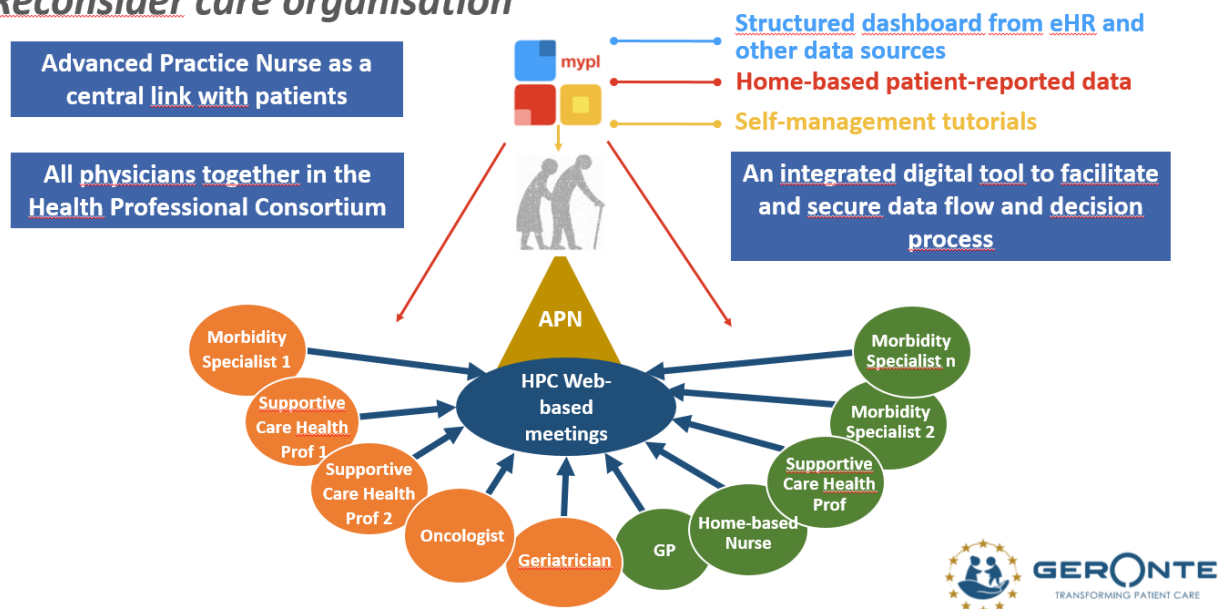
For optimal treatment decisions in the complex scenario of multimorbid patients, numerous existing medical, lifestyle and patient-reported data must be made available to health professionals at the time of treatment decision and patient follow-up. Although progress is hampered by the routine exclusion of multimorbid patients from clinical trials (Jadad JAMA 2011), it is widely accepted by clinicians that data required for treatment decisions include detailed evaluation of the patient's overall health status (including clinical background with multimorbidity, intrinsic capacity and patient preferences) which can be routinely performed by trained geriatricians using Comprehensive Geriatric Assessment (CGA). CGA is recognized as best practices for older cancer patients and is available through learned societies such as SIOG (Societe Internationale d'Oncologie Geriatrique), a Partner in the GerOnTe consortium. CGA is performed in patients with probable frailty according to a screening questionnaire such as G8 (Soubeyran Plos One 2014). The prognostic value of CGA in cancer patients has been demonstrated: CGA identifies patients at risk of early death (Soubeyran J Clin Oncol 2012), early functional decline (Hoppe J Clin Oncol 2013) and severe toxicities (van Walree J Ger Oncol 2019). Currently, too few patients benefit from CGA because it is

considered too time-consuming despite the fact that this assessment increases efficiency and cost-effectiveness by enabling avoidance of unnecessary procedures and treatments as well as complications (Hamaker J Clin Oncol 2017).

The clinical model behind GerOnTe is to regroup all health professionals taking care of a multimorbid patient, into a common care coordination pathway, the Health Professional Consortium (HPC). The HPC will (i) centralise the decisions, aligning them to the patient's priorities, (ii) be assisted by an Advanced Practice Nurse (APN) as case manager, and (iii) be facilitated by HolisTM GV data exchange, personalised for each patient. Patients will be stratified in order to determine their dominant disease, thus the appropriate HPC. Patient-centred health management by the HPC, with availability of real time, hospital- and patient-based data, will foster timely decisions enabling avoidance of unnecessary procedures and treatments leading to a reduction in the number of ineffective treatments, complications and unscheduled hospitalisations, concerted treatments of multimorbidities and to more patients staying at home thanks to self-management related reduction of dependence.

GERONTE patient-centred management

Reconsider care organisation



2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of GerOnTe TWOBE is to evaluate the effectiveness of the GerOnTe, ICT-based, integrated care pathway to improve patient 6-month quality of life, in Belgium and the Netherlands.

2.2. SECONDARY OBJECTIVES

The secondary objectives of GerOnTe TWOBE are, in the context of a Belgian and Dutch health-system organisation, to:

- Evaluate the effectiveness of the GerOnTe patient-centred system to:
 - Improve quality of life at 3, 9 and 12 months (secondary endpoint #1),
 - Improve patient survival and progression-free survival at 12 months (secondary endpoint #2),
 - Improve patient autonomy and minimize frailty and weight evolution at 3, 6, 9 and 12 months (secondary endpoint #3),
 - Reduce patient anxiety at 3, 6, 9 and 12 months (secondary endpoint #4),
 - Reduce patient unscheduled hospitalisations and patient institutionalisations at 6 and 12 months (secondary endpoint #5);
- Assess the cost-utility (through a cost-utility analysis – CUA) and the cost-effectiveness (through a Cost-Effectiveness Analysis – CEA) of the GerOnTe intervention versus standard of care up to 1-year post-inclusion (3, 6, 9 and 12 months after inclusion) (secondary endpoint #6);
- Evaluate caregiver burden in health, psychological well-being, finances, social life and relationship with patient at 3, 6, 9 and 12 months (secondary endpoint #7);
- Evaluate patient-reported overall experience of the GerOnTe intervention at 6 and 12 months post-inclusion (secondary endpoint #8);
- Evaluate patient and health care professionals reported overall satisfaction and acceptability of the GerOnTe intervention at 6 and 12 months (secondary endpoint #9);
- Analyze the implementation and use of the GerOnTe patient-centred intervention by patients and professionals (secondary endpoint #10).

2.3. ANCILLARY STUDY OBJECTIVE

The general objective of the ancillary study, as detailed in the appendix 1, is to support the economic, implementation evaluation, and the development of a business case of the GerOnTe model.

The specific objectives of this study are to:

1. Identify, describe, analyse, and map the common and distinctive elements of the current care pathways for older multimorbid patients (with cancer as a primary condition) in Belgium and the Netherlands within each clinical sites involved before the implementation of GerOnTe,
2. Describe and analyze the process of implementation of the intervention in the trial sites beyond the specific trial outcomes to enable analysis of the mechanism of action of the intervention, the contextual factors and barriers and facilitators to implementation (to develop a comprehensive implementation guide that will inform implementation across diverse settings).

In each clinical site, the ancillary study will involve approximately 3-5 staff members (e.g., principal investigator, clinicians, nurses, administrators) and 5-10 patients and/or family members/caregivers over the entire duration of the project.

3. STUDY ENDPOINTS

3.1. PRIMARY ENDPOINT

Quality of life assessed by the EORTC QLQ-C30 (version 3.0, appendix 2) questionnaire at 6 months after inclusion.

Three derived scores of the QLQ-C30 questionnaire are considered as primary endpoints:

- Normalized global health status score of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100),
- Normalized score of the physical functioning scale of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100),
- Normalized score of the emotional functioning scale of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100).

3.2. SECONDARY ENDPOINTS

1. Quality of life

- Normalized 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 after inclusion.
- Normalized scores of the following QLQ-C30 scales/items assessed at baseline, 3, 6, 9 and 12 months after inclusion: role functioning scale, cognitive functioning scale, social functioning scale, fatigue scale, nausea scale, pain scale, dyspnea item, insomnia item, appetite loss item, constipation item, diarrhea item and financial difficulties item.
- Scores of the following QLQ-ELD14 scales/items (appendix 3) assessed at baseline, 3, 6, 9 and 12 months after inclusion: assess mobility scale, worries about others scale, future worries scale, maintaining purpose scale, burden of illness scale, joint stiffness item, family support item. The QLQ-ELD14 questionnaire is a complementary module to the QLQ-C30 and taking into account the specific needs of older patients.

2. Survival

- Overall survival at 12 months after inclusion,
- Progression-free survival (PFS) defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.

3. Patient autonomy, frailty and weight evolution

- Dependence score of the Activities of Daily Living scale (Katz ADL) (appendix 4) assessed at baseline, 3, 6, 9 and 12 months after inclusion,
- Proportion of patients living at home at 6 and 12 months after inclusion,
- Number of completed chair stands in 30 seconds (Chair stand test: participants stand up repeatedly from a chair for 30 seconds) at baseline, 3, 6, 9 and 12 months after inclusion.,
- Score of the Clinical Frailty Scale (appendix 5) at baseline, 3, 6, 9 and 12 months after inclusion,
- Grade of performance status, measured by ECOG-PS (appendix 6) at baseline, 3, 6, 9 and 12 months after inclusion,
- Weight at baseline, 3, 6, 9 and 12 months after inclusion.

4. Patient anxiety

Score of HADS (appendix 7) at baseline, 3, 6, 9 and 12 months after inclusion.

5. Patient institutionalisation and unscheduled hospitalisations

- Proportion of patients institutionalised (see definition in section 7.1.3) at baseline, 6 and 12 months after inclusion.
- Proportion of patients with at least one unscheduled hospitalisation and number of unscheduled hospitalisations per patient (see definition in section 7.1.4) during 12 months after inclusion.

6. Cost-utility and cost-effectiveness analysis

- Cost per life years gained (CEA), cost per QALY gained (CUA) and incremental cost-effectiveness ratios (ICERs) obtained by a cost-utility and a cost-effectiveness analysis. Life years gained (LYG) in the CEA will be derived from a clinical metric (overall survival/progression-free survival) that will be measured at 6 and 12 months,
- Quality-adjusted life years (QALYs) in the cost per QALY gained (CUA) calculated using utility assessed through normalised scores of EQ-5D-5L questionnaire (appendix 8) collected at baseline, 3, 6, 9 and 12 months after inclusion. It includes the 5-level questions covering five dimensions.
- Resource use data during the 12 months of patient follow-up will include all direct and indirect costs and will be collected through:
 - Trial case report forms (CRFs) completed by the study collaborator or the APN,
 - Electronic medical records (EMRs) and electronic patient files linked to the patient sample by deterministic matching,
 - Patient questionnaires (e.g., patient report the frequency of visits to the medical specialist, APN, general practitioner). Questionnaires will be completed at baseline and at 3, 6, 9 and 12 months.
- Caregiver: questionnaire for the measurement, valuation and estimation of costs of informal care.
- Results will be presented as:
 - cost per life years gained (CEA),
 - cost per QALY gained (CUA),
 - Incremental cost-effectiveness ratios (ICERs).

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

Total burden will be obtained using the Zarit Burden Interview (Zarit et al, 1980; Hagell et al 2017) (appendix 9) by adding the scores across all 22 items, assessed at baseline, 3, 6, 9 and 12 months after inclusion.

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

Patient experience measured through the Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) - 11 items (Lloyd et al 2019) (appendix 10) and a question about worth of treatment, both at 6 and 12 months after inclusion.

9. Patient, physician and health-care-professionals-reported overall satisfaction with the IC technology of the GerOnTe intervention

Patient satisfaction and usability of mHealth application within the GerOnTe intervention will be evaluated by using the score derived from the 21-items mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (Zhou et al 2019) (appendix 11A and 11B) at 6 and 12 months after inclusion.

Physician and health-professional satisfaction and usability of mHealth application within the GerOnTe intervention will be evaluated by using the score derived from the adjusted version designed for health care providers of the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Provider version) (Zhou et al 2019) (appendix 12), consisted of 18 items, at 6 and 12 months after inclusion.

10. GerOnTe patient-centred system implementation and usage

GerOnTe patient-centred system implementation and usage will be evaluated at 6 months and 12 months after inclusion:

- Number and frequency of connections to the Holis Patient App,
- Duration of logins and activities with the Holis Patient App,
- 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 PROM's dashboards completed by patient,
- Number of health professional meetings (Multidisciplinary Tumour Boards (MTB) or other morbidities treatment decision) involving complete dashboards analysis by site.

Because no adverse event is expected to be generated by the GerOnTe intervention, the research protocol does not plan any assessment of traditional safety endpoints. However, the implementation and usage of the GerOnTe intervention, which are particularly important issues in understanding its effectiveness, will be carefully evaluated. As such, if any event that could be characterised as adverse event or serious adverse event (as defined in the section 12. MANAGEMENT OF ADVERSE EVENTS / SIDE EFFECTS / INCIDENTS) occurred, those events would be fully reported and described.

11. Ancillary study

Ancillary study is fully described in appendix 1.

4. STUDY DESIGN

4.1. TYPE OF TRIAL

Study design is a stepped wedge randomised controlled trial. Clusters will be participating hospitals, comprising eight investigating sites in total (Figure 2).

This is a stepped wedge of cross-over type. Patients included at each "step" are different individuals. The first "step" is a reference measurement where none of the clusters will implement the intervention. The investigating sites will be randomly drawn to determine the order in which they will implement the intervention, by "steps" of two months. A total of 10 patients by step are to be included in each centre; these 10 patients must be regularly included along the 2-month period of each step. If 10 patients are

already included before the end of the 2 months' step period, the centre has to stop the inclusions till the beginning of the subsequent step. If a centre, near to the end of a step, is far from reaching of the 10 patients' inclusion, it must increase the speed of its inclusions to be as close as possible of 10 patients included at the end of the step. In each centre, patient sample has to be representative of type of cancer managed in the centre, along the trial duration. The repartition of cancer types must be homogeneous along the steps and during the trial duration. Descriptive analyses of patient sample by center will be done post hoc in order to check representativity of the samples.

All participating investigating sites will have study collaborators in charge of organizing intervention implementation and data collection. The intervention will be prepared prior to the start of the trial, so that each investigating site can implement it as defined by the randomisation. Each centre engaged to participate needs to participate till the end of the trial. A centre commitment to participate will be requested before each centre involvement to avoid centre withdrawal after the start of the trial. Quantitative data regarding the Holis Patient App usage will be collected at each step and in each cluster by study collaborators, from the beginning of GerOnTe intervention implementation. Care outcome data (Quality of life, anxiety, autonomy, additional hospitalisation, mortality...) will be collected by local referents at baseline and at 3, 6, 9 and 12 months after inclusion in GerOnTe. The data necessary to calculate the real cost of the intervention, of its implementation and of resource use data of patient management will be continuously collected during follow-up. GerOnTe patient-centred intervention implementation and usage will be collected by the local referents in each centre. Qualitative analysis will be performed in each centre at GerOnTe intervention implementation and during follow-up.

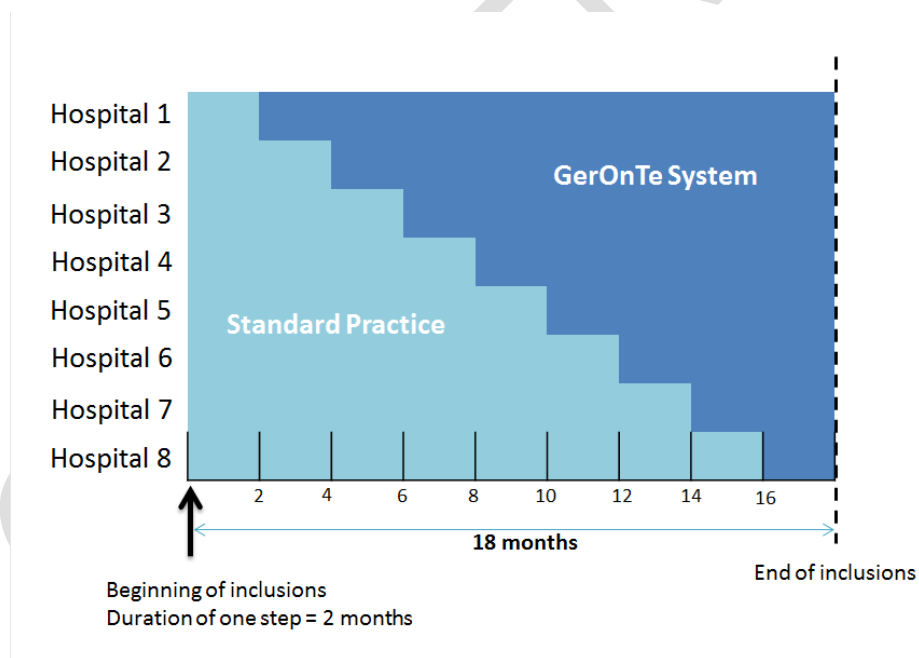


Figure 2: Schematic representation of GerOnTe TWOBE stepped wedge cross-designed for inclusion of 720 patients across eight sites.

The randomisation list will be established by the statistician at the Methodology and Data Management Centre of Institut Bergonié prior to the start of the research using SAS software. A document describing the randomisation procedure will be kept confidential within the Methodology and Data Management Centre of Institut Bergonié.

In this stepped wedge trial, the order of integration of the intervention in the sites will be randomised. The intervention will be implemented in a single site at each "step" to ensure optimal power. The centres will be informed at the outset when the intervention will be implemented.

4.2. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 30 months, including about 18 months of active enrollment.

Planned start date (first participant on study): December 2022.

The planned study termination (clinical cutoff) corresponds to the date when each participant has been followed-up for 12 months or is deceased.

End of study occurs when all of the following criteria have been satisfied:

- The trial is closed to enrollment

AND

- The last included participant has been followed for 12 months or if deceased, each participant has been followed-up for 12 months or is deceased.

4.3. DEFINITIONS OF DURATION OF STUDY PER PARTICIPANT

Depending on the period (light or dark blue on the figure 2), participants will be included either in the control arm (light blue) or in the intervention arm (dark blue).

Participants will be evaluated at scheduled contact moments as described in section 7.

Each participant will be followed-up for 12 months after inclusion.

To have a real overview of the outcome of multimorbid patients, especially about survival and institutionalisation, a longer follow-up is highly relevant. Therefore, we plan to monitor patients' vital status and living situation until 5 years after inclusion. This follow-up is additional and not mandatory to fulfill our main objectives. It will be conducted only if financial support is retrieved.

Participants will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period.

Participants may withdraw their consent at any time; no further study activities will be conducted on them.

Study discontinuation occurs when an enrolled participant ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in section 7). Participants have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.

The date and reason for study discontinuation will be clearly documented in the participant's eCRF.

5. SELECTION OF PATIENTS

5.1. INCLUSION CRITERIA

General inclusion criteria

1. Age \geq 70 years old,
2. New or progressive cancer (breast, lung, colorectal, prostate) fulfilling the tumour specific inclusion criteria,
3. Estimated life expectancy greater than 6 months,
4. At least one moderate/severe multimorbidity inclusion criteria other than current cancer (see separate list under 5.3),
5. Patients must be willing and able to comply with study procedures,
6. Voluntarily signed and dated written informed consents prior to any study specific procedure,
7. QLQ-C30 Quality of Life Questionnaire fully completed at baseline, before inclusion.

Tumour specific inclusion criteria

8. Specific inclusion criteria for **breast cancer:**

8.1. Non-metastatic breast cancer (M0):

- No prior treatment for the current breast cancer.
- All 3 criteria required:
 - Clinical staging: cT2-3-4 Nany, or cTany N1-2-3,
 - The cancer specialist considers* surgery,
 - The cancer specialist considers* radiotherapy and/or chemotherapy.

8.2. Metastatic breast cancer (M1): Both criteria required:

- The cancer specialist considers* chemotherapy or PARP-inhibitors or mTOR-inhibitors / PIK3CA inhibitors; Previous endocrine therapy +/- CDK4/6 inhibitors is allowed,
- The patient received maximum 1 prior line of chemotherapy for metastatic disease.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

9. Specific inclusion criteria for **colorectal cancer:**

9.1. Non-metastatic colorectal cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital.
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery,
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* chemotherapy.

9.2. Metastatic colorectal cancer (M1):

- The cancer specialist considers* first line systemic therapy and/or radiotherapy (+/- surgery). No previous chemotherapy allowed except adjuvant/perioperative chemotherapy stopped for more than 12 months.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

10. Specific inclusion criteria for **lung cancer:**

10.1. Non-metastatic lung cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital.
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery (patients considered for treatment with percutaneous thermoablation alone are not eligible),
 - The cancer specialist considers* radiotherapy (except SBRT),

- The cancer specialist considers* systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

10.2. Metastatic lung cancer (M1):

- The cancer specialist considers* first or second line systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

11. Specific inclusion criteria for prostate cancer:

11.1. Non-metastatic prostate cancer (M0): one of the following:

- First diagnosis M0 prostate cancer (no therapy received yet for prostate cancer): at least one of the 2 criteria required:
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* hormone therapy (ADT +/- combination Abiraterone and Prednisone).
- Salvage treatment M0 prostate cancer (received prior surgery at least 6 months before):
 - The cancer specialist considers* radiotherapy (+/- ADT).
- Non-metastatic castration resistant prostate cancer:
 - The cancer specialist considers* treatment intensification (ADT + Enzalutamide or Apalutamide or Darolutamide).

11.2. Metastatic prostate cancer (M1):

- The cancer specialist considers* treatment with Abiraterone or Enzalutamide or Apalutamide, or Docetaxel or Cabazitaxel or PARP-inhibitors or Lutetium PSMA.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

5.2. EXCLUSION CRITERIA

1. Mental illness/cognitive impairment that limits ability to provide consent or complete trial procedures.
2. Participating to an interventional clinical trial with a non-registered anticancer drug or to another geriatric intervention trial.
3. Patients and caregivers are unable or unwilling to use ICT-devices (tablet, computer, smartphone) or the Internet according to protocol.
4. Patient already included in this study.

5.3. SEVERE MORBIDITY CRITERIA

Patient must be fulfilling one or more of the criteria below:

General

1. Two or more unscheduled comorbidity related hospitalisations in the past year (not related to index cancer).
2. Having received out-patient care from two more specialties in the past year (not related to index cancer).

Cardiac

3. Any prior symptomatic myocardial infarction.
4. Any past valve replacement, percutaneous coronary intervention), percutaneous transluminal coronary angioplasty) or coronary artery bypass graft.
5. Congestive heart failure under follow-up by a cardiologist.
6. Chronic exertional angina.
7. Regular use of anti-anginal medication.
8. Left ventricular hypertrophy.
9. Dyspnoea or activity restriction secondary to cardiac status.
10. One or more admissions to hospital for cardiac reasons in past year.

Vascular

11. Previous vascular intervention.
12. Symptomatic atherosclerotic/peripheral vascular disease.

Venous

13. Any history of pulmonary embolism.
14. Use of coumadin/warfarin, heparin, DOAC or NOAC with indication venous disease.

Hypertension

15. Need of three or more types of blood pressure medication.

Haematopoietic

16. Any chronic hematologic disease.
17. Haemoglobin: <10 g/dL (6.0 mmol/l) (not related to index cancer).

Endocrine

18. Insulin dependence.
19. Diabetes-related complications (retinopathy, neuropathy, nephropathy, coronary artery disease or peripheral arterial disease).
20. Poorly controlled diabetes mellitus or diabetic coma in the past year.
21. Requires adrenal hormone replacement.

Pulmonary

22. Dyspnoea at rest.
23. Limited activities secondary to pulmonary status.
24. Requires oral steroids for lung disease.
25. One or more admissions to hospital for pulmonary reasons in past year.
26. Two or more hospitalisations for pneumonia in past five years.

Renal

27. eGFR < 30 ml/min.

Hepatobiliary

- 28. Chronic hepatitis.
- 29. Cirrhosis.
- 30. Portal hypertension with moderate symptoms.
- 31. Compensated liver failure.
- 32. Clinical or lab evidence of biliary obstruction (not related to index cancer).
- 33. Acute or chronic pancreatitis or hepatitis in past 5 years.

Stomach/intestine

- 34. Recent ulcers (<6 months) or any history of ulcers requiring hospitalisation.
- 35. Any history of inflammatory bowel disease.
- 36. Any swallowing disorder or dysphagia.
- 37. Chronic diarrhoea (not related to index cancer).
- 38. Bowel impaction in the past year (not related to index cancer).
- 39. Status post bowel obstruction (not related to index cancer).
- 40. Ostomy/stoma in situ (not related to index cancer).

Nutrition and weight

- 41. Weight loss more than 6 kg in past six months.
- 42. Weight loss more than 3 kg in past 1 month.
- 43. Significantly decreased food intake.
- 44. Body mass index < 19 kg/m².
- 45. Body mass index > 38 kg/m².

Neurologic

- 46. Status post cerebrovascular accident (CVA) with at least mild residual dysfunction.
- 47. Any past central nervous system neurosurgical procedure.
- 48. Neurodegenerative disease including Parkinson's disease, parkinsonism, multiple sclerosis, myasthenia gravis etc.).
- 49. Requires daily meds for chronic headaches or headaches that regularly interfere with daily activities.

Sensory

- 50. Partially or functionally blind, unable to read newsprint.
- 51. Functional deafness or conversational hearing impaired despite hearing aid.
- 52. Laryngectomy.

Mobility

- 53. Requires a walking aid/wheelchair.
- 54. Difficulties in activities of daily living secondary to mobility impairment.
- 55. Difficulty walking >100m without resting.
- 56. Requires steroids or immunosuppressant medication for arthritic condition or connective tissue disease.
- 57. Prior or current symptomatic vertebral compression fractures from osteoporosis.

Psychiatric

- 58. Active substance abuse with social, behavioural or medical complications.

- 59. History of schizophrenia or another psychotic disorder.
- 60. Requires daily antipsychotic medication.
- 61. Current usage of daily anti-anxiety medication.
- 62. Currently meets DSM criteria for major depression or bipolar disorder.
- 63. One or more episodes of major depression in the past 10 years.
- 64. Any previous psychiatric hospitalisation.

Cognition/Delirium

- 65. One or more prior deliriums in the past 10 years.
- 66. Cognitive impairment that does not inhibit patient to provide informed consent and understand study procedures.

Previous cancer

- 67. Another type of cancer than the index cancer with at least one of the following criteria:
 - Required chemotherapy or radiation therapy in the past 5 years,
 - Non-curable and/or metastatic cancer.

Instrumental Activities of Daily Living (iADL)

- 68. Care dependent in one or more aspects of the following instrumental activities of daily living (preparing meals, walking outside alone, managing medication).

Social

- 69. Patients has no or very limited support system or informal caregivers.

6. STUDY INTERVENTION GERONTE-SYSTEM

6.1. INTERVENTION DESCRIPTION

The intervention will include the following components, which will be elaborated on in sections 6.2 to 6.6 and figures 3 and 4.

- A health professional consortium (HPC) for each patient, which will work together to make recommendations regarding oncologic treatment and non-oncologic interventions, at baseline and in the course of treatment. This will be in addition to the usual multidisciplinary tumour board (MTB) which will provide an oncologic treatment recommendation based on the usual oncologic work-up.
- An advance practice nurse (APN) as case-manager, who will be the primary contact person for the patient during the oncologic treatment and subsequent follow-up.
- A baseline patient evaluation consisting of a comprehensive geriatric assessment (CGA) by a geriatrician, APN or trained study collaborator, which will focus on general health status, comorbidities and intrinsic capacity. Baseline documentation of patient preferences and priorities will be collected by the APN.
- A health care professional dashboard, called Holis Dashboard, which 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 the standard consensus dataset. Dashboard data will be made available selectively to all health care professionals of the HPC.

- A patient monitoring application called Holis Patient App, which will allow for monitoring of symptoms and signs of destabilised comorbidity or functional decline during and after treatment, with additional self-management library with recommendations for how the patient can deal with issues or for contacting their health care professionals in case of symptoms requiring urgent intervention.
- Additional data (paper questionnaires and test) will be collected every 3 months and are listed under sections 7.2 and 7.3.

6.2. HEALTH PROFESSIONNAL CONSORTIUM (HPC)

For each patient, a HPC is constructed based on the needs of the specific setting of the patient, but at minimum consists of a cancer specialist, a geriatrician and an APN. Additional input from other health care professionals, including the general practitioner, will be gathered by the APN prior to HPC meetings if these professionals are not able to join the HPC themselves. In brief, the HPC meets before the final treatment decision is made with the patient. The first HPC takes place within 15 days of inclusion. At 3, 6, 9 and 12 months (+/- 15 days), there are fixed follow-up meetings, but additional HPC meetings can be planned as needed in case of changes in the patient situation. The APN is responsible for the coordination of the HPC meetings.

6.3. MULTIDISCIPLINARY TUMOUR BOARD (MTB)

The MTB will be executed as per standard of care for each hospital.

6.4. ADVANCE PRACTICE NURSE (APN)

The advance practice nurse will play a central role in the care for the older patients with multimorbidity and cancer. The APN will do the inclusion for the clinical trial during the intervention phase, will collect additional information regarding patient's social situation, priorities and preferences, will organize the HPC meetings at regular intervals, will monitor patients during treatment based on the Holis Patient App and will initiate non-oncologic interventions based on the recommendations of the HPC.

6.5. HOLIS MEDICAL DEVICE

According to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR) and Medical Device Coordination Group (MDCG) 2019-11, Holis™ GV is a software considered a non CE marked medical device class IIa. The device is a standalone software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes.

The Holis™ GV medical device is a platform with two applications:

- Holis Dashboard is built for the health care professionals participating in the GerOnTe TWOBE clinical trial, consisting of a decision-making dashboard and a care trajectory dashboard. The decision-making dashboard represents clearly all relevant information about the patient that is necessary for health care professionals to provide a treatment recommendation. The care trajectory dashboard is

developed for the health care professionals to follow up the patient situation with regards to different events that may occur during the care trajectory. Holis Dashboard is designed for health care professionals, in particular APNs, geriatricians and oncologists.

- Holis Patient Application is built for patients and caregivers participating in the GerOnTe TWOBE clinical trial. The Holis Patient App allows patients to register daily/weekly/monthly his/her symptoms. In addition, patient-tailored self-management recommendations are proposed via the app based on the reported symptoms. Holis Patient App is developed for patients aged 70 years and older, with cancer and at least one other disease ("multimorbid" patients).

Further details regarding the description of Holis™ GV can be found in the latest version of the Investigator's Brochure.

The manufacturer of Holis™ GV is MyPL, My Personal Lifescope, based in Montigny-le-Bretonneux, France. MyPL has experience in the development of software in support of the multidisciplinary approach to patients with cancer. More information on the manufacturer of Holis™ GV can be found in the document TD-Holis-1.0-Detail on the manufacturer_v0.0_20220624.

The following identification data belong to Holis™ GV medical device:

Trade name	Holis™ GV
Version	V1
Basic UDI-DI	None
EMDN code	V92
GMDN code	None
Manufacturer	MYPL

Holis™ GV is meant to provide an accurate vision of the patient profiles included in the clinical trial, for all health care professionals to provide a fair and accurate treatment recommendation and patient-tailored advice at any time during the trial phase. The intended purpose of Holis™ GV is to build the relevant dashboards that will help:

- all stakeholders interact together,
- to share information that is useful to make proper decisions,
- to consider patient's preference in terms of living longer, preserving independence, reducing symptoms or limiting treatment risks,
- to understand how the patient's health evolves over time based on real-time patient's symptoms (new comorbidities, weight loss, cognitive impairment...) and PROMs, leading to early intervention in case of new event reporting.

The health care professionals involved in this clinical trial will receive a training in order to use the Holis™ GV medical device properly.

6.5.1. Holis Dashboard description and functionalities

The components of the decision making Holis Dashboard include:

- An image of the patient,
- Personal data (including primary care giver and general practitioner information),
- Information about the living and social situation,
- Minimal oncological dataset,
- Information about comorbidities including severity and impact on daily life,
- Information about prognosis (non-cancer related),
- Intrinsic capacity evaluation (defined by the WHO as the description of all the individual-level attributes that might contribute to healthy aging) by the geriatrician,
- Patient priorities and preferences,
- Decision control preferences evaluated by the patient,
- Information about medication and allergies,
- Input from other health care professionals,
- Decision making checklist and report (standardised form).

The components of the follow-up dashboard additionally include:

- Symptom monitoring information from the Holis Patient App,
- Questions from the patient to the APN or HPC,
- Treatments (oncological and non-oncological) and hospitalisations,
- **Overview of past and future HPC-meetings.**

The data will be completed on the Holis Dashboard via a secured external website accessible by health care professionals with access codes.

Additional functionalities include reminders for planning HPC meetings and for incomplete data.

6.5.2. Holis patient App description and functionalities

The components of the Holis Patient App are:

- Symptom monitoring tailored to the tumour type and treatment,
- 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,
- Space for personal notes,
- And the possibility to set up reminders for completing the symptom monitoring.

Holis Patient App can be installed on following ICT-devices: smartphone, digital tablet, computer (windows and apple).

For patients without ICT-device (estimated to 10% of the patients) in order to avoid discrimination, a digital tablet will be provided for the duration of the study (with Holis Patient App installed and WIFI internet subscription when necessary).

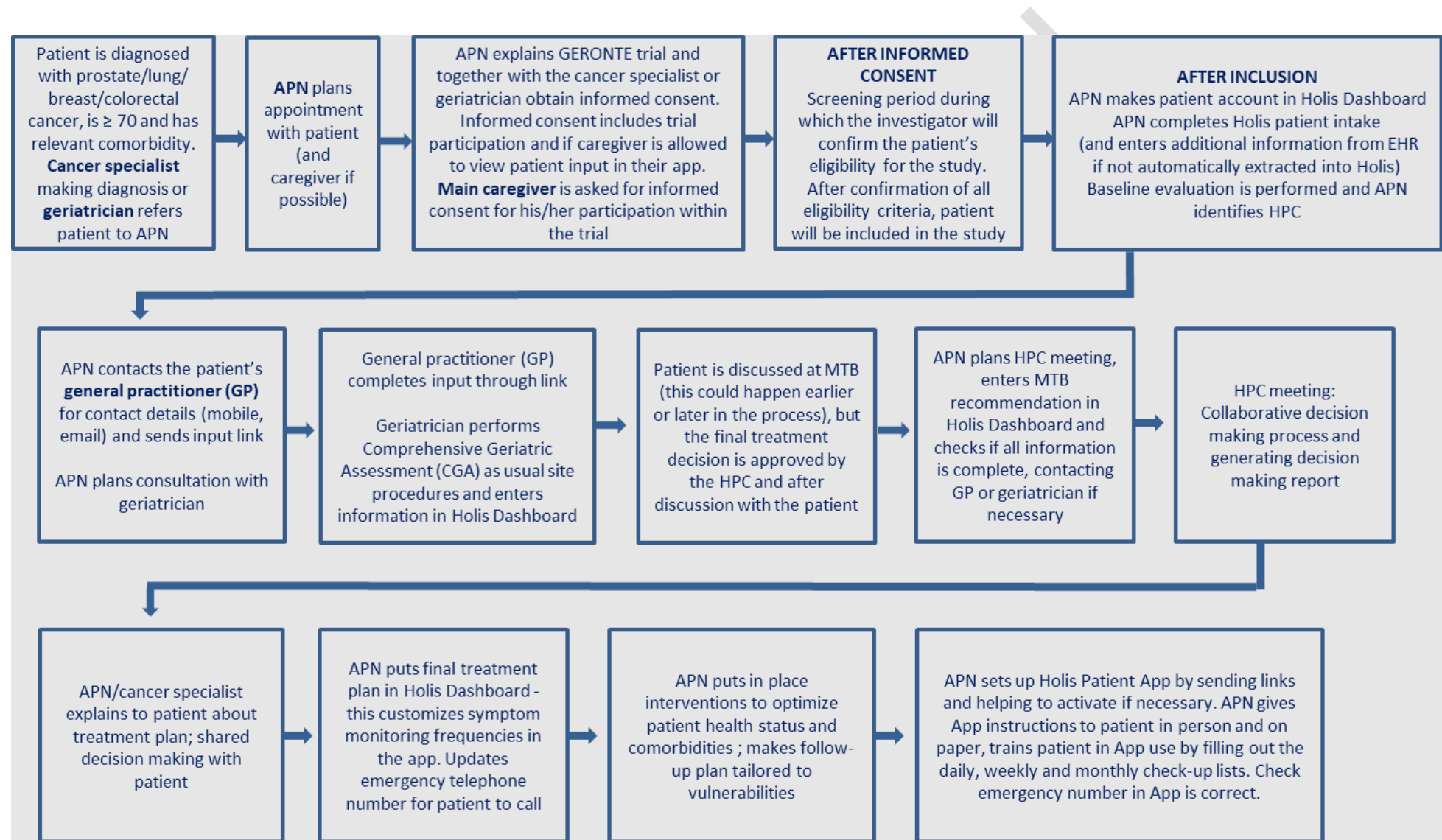
6.5.3. Device accountability

Adequate procedures for the accountability of Holis Patient Application, like control of access to the device, adequate storage of the device and the return of unused, expired or malfunctioning devices, are not applicable for the device used in this clinical trial.

During the clinical trial, an overview of all patients in the intervention arm and/or their caregivers with the Holis Patient Application installed and in use on their smartphones, tablets or computers will be kept by the principal investigators for traceability purposes. This overview consists of the name(s) of person(s) of the investigation team who received/used/returned or disposed the device, identification of the medical device, subject identification number, the date or time period of use by subject and the date on which the investigational device was returned or disposed. The overview will be updated each time a patient and/or his/her caregiver has entered and/or completed the clinical trial, wishes to discontinue his/her participation in the clinical trial or has died. Users of the Holis Patient Application can be quickly contacted in case of emergency situations related to the digital application.

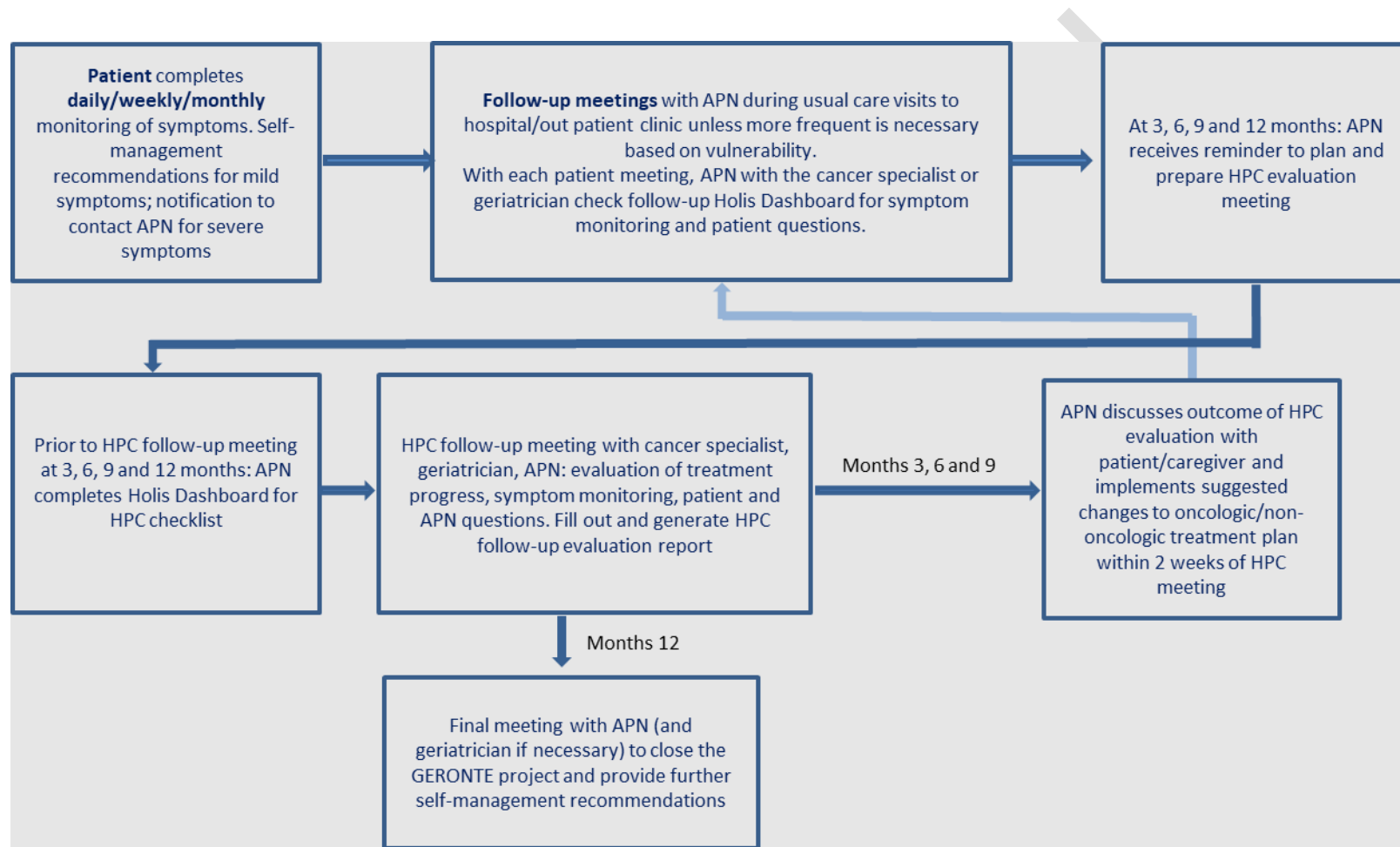
The Holis Patient Application will be installed by the patient and/or caregiver themselves, under supervision of a study collaborator if necessary, on their smartphone, tablet or computer. When a patient and/or caregiver is approached and included in the clinical trial, a study collaborator will give the necessary instructions for a correct use of the Holis Patient Application.

Each participating centre has a limited number of tablets available to loan to patients. The number of available tablets is in proportion to the total number of intervention patients in the intervention arm of the clinical trial. If the patient does not have the necessary computer equipment, the participating centre where the patient is being treated may be able to provide the patient with a connected digital tablet and internet access for the duration of the study without any additional costs. The principal investigators will also keep an overview of the patients to whom a tablet has been loaned. This tablet will be installed and handed over during the APN consultation at the start of the clinical trial. The tablet will be returned when the patient has reached the end of participation in the clinical trial regardless the reason (eg. withdrawal of consent, death,...).

Figure 3 : For intervention arm: inclusion and decision making

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Figure 4 : For intervention arm: during and after treatment



7. PATIENTS' MANAGEMENT

7.1. DEFINITION OF SPECIFIC STUDY TERMS

7.1.1. Study collaborators

Study collaborators will conduct patient assessments.

Study collaborators include clinical research assistants, nurses and any health care professional involved in the study.

Medical assessments will be performed by health care professionals (cancer specialist, geriatrician, nurse...).

Self-questionnaires will be given to the patient by a study collaborator (most often by a clinical research assistant, nurse and according to the habits of each site).

Other questionnaires and tests will be conducted by a study collaborator (most often by a health care professional or a study collaborator and according to the habits of each site).

7.1.2. Patient's caregiver

The informal caregiver is a person who provides assistance to a dependent and/or disabled person, generally part of their close circle of the patient (family member such as spouse or husband, ascendants, descendants, etc.) or a person that the patient has chosen (with a close and stable relationship with the person being cared for). The help provided is non-professional.

At the beginning of the study, the patient will be asked to identify his or her informal caregiver. If there is more than one, he/she will choose a primary caregiver for the study.

7.1.3. Institutionalisation

Institutionalisation means that a patient moves permanently to an institution among which are considered retirement houses.

7.1.4. Unscheduled hospitalisation

Unscheduled hospitalisation includes any hospitalisation which has not been previously planned because of an unscheduled event (severe adverse event, complication of treatment, decompensation of morbidity) whatever it is linked or not to the emergency room.

7.2. CONTROL ARM EVALUATIONS

	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)
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 scale)**		X	X	X	X	X
Anxiety and depression scale (HADS)*		X	X	X	X	X
Patient Caregiver Information**		X	X	X	X	X
Worth of treatment*				X		X
Unscheduled hospitalisations**	<-----X----->					
Patient institutionalisation**	<-----X----->					
Patient experience (P3CEQ)*				X		X
Intention to use (Modified version of MAUQ)*				X		X
Resource use (direct and indirect costs) */**		X	X	X	X	X
Ancillary studies**	<-----X----->					

* Self-administrated questionnaires

** Questionnaires and tests conducted by a study collaborator

7.2.1. Screening evaluation and informed consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. During the screening period and before inclusion, the Investigator will confirm the participant's eligibility for the study. The screening period will not exceed 28 days.

7.2.2. Baseline assessment

After confirmation of all eligibility criteria and upon request, eligible participants will be included in the study centrally at the KU Leuven/UZ Leuven as described in a specific SOP provided by the Sponsor.

The baseline period is accepted within a week between informed consent and inclusion.

The following assessments will be done:

- Medical history, baseline condition including comorbidities (*conducted by a study collaborator*),
- Assessment of baseline signs and symptoms (*conducted by a study collaborator*),
- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Concomitant treatments (number only) (*conducted by a study collaborator*),
- Demographic data (i.e. sex, age, height and weight) (*declared by the patient*),
- Cancer information (*conducted by a study collaborator*):
 - Date of diagnosis of the primary disease,
 - Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), if applicable,
 - Current cancer characteristics and treatments,
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Patient institutionalisation (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver (link with the patient, date of birth and initials) (*conducted by a study collaborator*),
- Collection of information regarding resource use (informal caregiver, home support, transport) (as listed under Section 10).

7.2.3. Patient management and follow-up

Each patient will be followed up to 12 months.

Every 3 months during one year, the following assessments will be done:

- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Demographic data (only weight) (*declared by the patient*),
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Cancer information (current cancer characteristics and treatments) (*conducted by a study collaborator*),
- Patient institutionalisation (*conducted by a study collaborator*),
- Unscheduled hospitalisations (date, reason and location) (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver: same since baseline or change (*conducted*

by a study collaborator).

- Patient-reported overall experience (Person-Centred Coordinated Care Experience Questionnaire-P3CEQ, appendix 10) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Worth of treatment only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Intention to use: mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (appendix 11B) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Resource use (direct/indirect costs) as listed under section 10 (*patient self-administrated paper questionnaire*),
- Ancillary studies: please refer to appendix 1.

In case of **study discontinuation**, the date and reason of will be recorded on the participant's CRF.

Participants who **withdraw consent** will not be followed with any study procedures.

7.2.4. End of participation

At the end of the 12 months of the GerOnTe intervention implementation, a study collaborator will inform the patients of their end of participation.

7.3. INTERVENTION ARM EVALUATIONS

	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)
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
APN consultation + assessments		X				
CGA (Comprehensive Geriatric Assessment as usual site procedures)**		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 scale)**		X	X	X	X	X
Anxiety and depression scale (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----->					
Holis Patient App completion*	<-----X----->					
Patient experience (P3CEQ)*				X		X
Intention to use (Modified version of MAUQ)*				X		X
Resource use (direct and indirect costs) */**		X	X	X	X	X
Ancillary studies**	<-----X----->					

* Self-administrated questionnaires

** Questionnaires and tests conducted by a study collaborator

7.3.1. Screening evaluation and informed consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. During the screening period and before inclusion, the Investigator will confirm the participant's eligibility for the study. The screening period will not exceed 28 days.

7.3.2. Baseline assessment

After confirmation of all eligibility criteria and upon request, eligible participants will be included in the study centrally at the KU Leuven/UZ Leuven as described in a specific SOP provided by the Sponsor.

The baseline period is accepted within a week between informed consent and inclusion.

The following assessments will be done:

- Medical history, baseline condition including comorbidities (*conducted by a study collaborator*),
- Assessment of baseline signs and symptoms (*conducted by a study collaborator*),
- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Concomitant treatments (number only) (*conducted by a study collaborator*),
- Demographic data (i.e. sex, age, height and weight) (*declared by the patient*),
- Cancer information (*conducted by a study collaborator*):

- Date of diagnosis of the primary disease,
- Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), if applicable,
- Current cancer characteristics and treatments,
- APN consultation and assessments (*see section 7.3.3.*),
- CGA (Comprehensive Geriatric Assessment as usual site procedures) assessing **general health status, intrinsic capacity, documentation of patient preferences, and oncological work-up (MTB)** (*conducted by a study collaborator*),
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Patient institutionalization (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical frailty scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's main caregiver (link with the patient, date of birth and initials) (*conducted by a study collaborator*),
- Collection of information about the patient's general practitioner (contact details to send input link) (*conducted by a study collaborator*),
- Collection of information regarding resource use (informal caregiver, home support, transport) as listed under section 10.

7.3.3. APN consultations and assessments

APN first contact

The aim of this first contact between APN and patient, and caregiver if possible, is to identify the HPC (including APN, geriatrician, oncologist, general practitioner (GP), home-based nurse, specialists according to other coexisting diseases and supportive care professionals), to train patients and caregivers on Holis Patient App usage and to upload patient's treatment preferences in the Holis Dashboard.

APN consultation and assessments in collaboration with a physician as needed

- For patient and caregiver,
- Outlining multimorbidity-informed treatment decision (and possible patient access to data through the Holis Patient App),
- Training in Holis Patient App usage,
- Advising on self-management when intrinsic capacity allows it,
- Collecting contact information of the patient's general practitioner and send him/her the link to complete information.

7.3.4. Patient management and follow-up

Each patient will be followed up to 12 months.

Every 3 months during one year, the following assessments will be done:

- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Demographic data (only weight) (*declared by the patient*),
- Quality of life (EORTC QLQ-C30, appendix 3) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),

- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Cancer information (current cancer characteristics and treatments) (*conducted by a study collaborator*),
- Patient institutionalization (*conducted by a study collaborator*),
- Unscheduled hospitalisations (date, reason and location) (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver: same since baseline or change (*conducted by a study collaborator*).
- Patient-reported overall experience (Person-Centred Coordinated Care Experience Questionnaire-P3CEQ, appendix 10) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Worth of treatment only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Intention to use: mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (appendix 11A) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Ancillary studies: please refer to appendix 1.

Collection of symptoms and adverse events on Holis Patient App

- Frequency varies depending on the symptom and the treatment between daily, weekly and monthly.
- Registration of hospitalisations in the web-based Holis Dashboard.

The patient will receive:

- self-management advice based on their symptom reporting,
- emergency contact details and prompts to call a medical team member for specific symptomatic treatment depending on severity.

The data are centralised in Holis Dashboard and used for subsequent actions.

In case of **study discontinuation**, the date and reason of will be recorded on the participant's eCRF.

Participants who **withdraw consent** will not be followed with any study procedures.

7.3.5. End of participation – end of GerOnTe intervention implementation

At the end of the 12 months of the GerOnTe intervention implementation, a study collaborator (mostly the APN) will inform the patients of their end of participation. She/he will also proceed, within one month of the last **loading in Holis Patient App**, to the remote uninstallation of the application.

In case of a tablet loan, the APN will also organize the return of the equipment.

In the event of the patient's death occurs before 12 months and within one month of the death, the APN will contact the family again in order to remotely uninstall the application. In case of a tablet loan, the APN will also organize the return of the equipment.

7.4. EARLY DISCONTINUATION OF THE STUDY

In case of early closure of the research, inclusions will be definitely stopped but, as defined in section 4.2, end of study will occur when all patients have stopped study procedure and the last included patient has been followed for 12 months or if deceased, each participant has been followed-up for 12 months or is deceased.

7.5. SPECIAL SITUATIONS DURING THE STUDY

It is important to note that the following situations do not result in the patient's discontinuation of the study:

- Progression of the disease,
- Change of treatment line.

Visits and assessments should be maintained as per protocol.

8. CAREGIVER'S MANAGEMENT

Written informed consent for the primary caregiver's participation in the study must be obtained prior to conducting any study-specific questionnaires.

Primary caregiver may be involved in three different ways:

- For all caregivers:
 - Zarit burden interview (ZBI, appendix 9) to evaluate the caregiver burden (caregiver *self-administrated paper questionnaire*),
 - Questionnaire for the measurement, evaluation and estimation of costs of informal care.
- For a sample of caregivers: the ancillary study (appendix 1).

For both control and intervention arms, all main caregivers will be asked to complete the Zarit burden interview through paper questionnaires, and the questionnaire for the measurement, valuation and estimation of costs of informal care at baseline, 3, 6, 9 and 12 months after inclusion.

9. PHYSICIAN AND HEALTH CARE PROFESSIONALS' MANAGEMENT

Written informed consent for the physician and health care professionals' participation in the study must be obtained prior to conducting any study-specific questionnaires.

Physician and health care professionals may be involved in two different ways:

- For all physician and health care professionals in the HPC: MAUQ questionnaire (appendix 12) to evaluate physician and health-care-professionals-reported overall satisfaction with the application of the GerOnTe intervention (physician and health care professional *self-administrated paper questionnaire*).
- For a sample of physician and health care professionals: the ancillary study (appendix 1).

Physicians and health professionals in the HPC will be asked to complete the adjusted version of the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Provider version). The questionnaire will be administered through paper questionnaire at 6 and 12 months after inclusion of the first intervention arm patient.

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10. RESOURCE USE MANAGEMENT

To perform the economic evaluation, we will collect total costs, which are broken down into direct costs, either medical or non-medical, and indirect costs. These resource data will be collected for both control arm and intervention arm.

Resource use data will be collected until 12 months post-inclusion in the trial through different sources:

- Trial case report forms (CRFs) completed by the study collaborator or the APN every three months,
- Electronic medical records (EMRs) and electronic patient files linked to the patient sample by deterministic matching,
- Patient questionnaires (e.g., patient report the frequency of visits to the medical specialist, APN, general practitioner),
- Questionnaire/interview for cost outside the clinical site, direct non-medical costs and indirect costs.

Resource use data, questionnaires and interviews will be completed at baseline and at 3, 6, 9 and 12 months. A three-month interval is a suitable time for minimizing recall bias and the questionnaire burden.

Direct medical costs related to intervention (for intervention arm only) will be collected using TDABC methodology and Business case / estimates (for intervention).

All resource use will be valued in monetary terms using appropriate unit costs or participant valuations estimated at the time the trial starts.

Category	Resources
Direct medical costs	
Hospital-based services	Hospitalisations, medical goods, procedures
Pharmaceutical consumptions	Medicinal products, medicinal devices
Personnel	Medical time, APN time, MTB time, other
Emergency department	Unscheduled visits to the emergency room, procedures performed, use of ambulance, other
Outpatient care	Medical consultations, medical imaging, other
Intervention (for intervention arm only)	Training, equipment, MTB time, other
Direct non-medical costs	
<ul style="list-style-type: none"> • Travel expenses • Community care/formal care 	
Indirect costs	
<ul style="list-style-type: none"> • Caregiver productivity loss • Unpaid caregivers' labour (informal care) 	

Synthesis for patient questionnaires at baseline and at 3, 6, 9 and 12 months:

- Hospitalisations if outside the clinical site,
- Procedures (e.g. surgery, medical imaging) if outside the clinical site,
- Unscheduled visits to the emergency room,
- Medical consultations (e.g. visit to GP, psychologist, nurse),
- Travel expenses (e.g. taxis, personal vehicles, public transports, etc),
- Community care/formal care (e.g. home help)

Synthesis for caregiver questionnaire at baseline and at 3, 6, 9 and 12 months:

- Caregiver productivity loss (e.g. how many hours did the caregiver miss from work due to relative's disease or condition),
- Unpaid informal care (e.g. time spent on household activities or unpaid activities).

Synthesis concerning the data collection performed by the study collaborator for the clinical site (information that concern only the clinical site and if possible, other services than oncology):

- Hospitalisations (e.g., reason for hospitalisation, bed-days, length of stay),
- Procedures (e.g., surgery, medical imaging),
- Medicinal products (e.g., drugs, medical devices),
- Unscheduled visits to the emergency room.

11. STATISTICAL CONSIDERATIONS**11.1. HYPOTHESES AND NUMBER OF PARTICIPANTS NEEDED**

Sample size calculations were drawn in order to be able to detect a mean difference of 10 points or more (on a score from 0 to 100) (Osoba 1998), should the intervention be effective, for at least one of the three targeted health-related quality of life (HRQoL) scores (common standard deviation of 20 points). Each of the three scales will be independently tested. With a 1.6% two-sided type I error and a statistical power of 90%, the minimum number of patients to include is 222. Accounting for a possible 20% dropouts, the total minimum number of patients to be included is 278. 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 corresponding to 10 patients on average per step and per centre (Table 2.1)

Randomized investigating sites	Number of patients to include per step	Total Nb of patients to include control arm	Total Nb of patients to include Intervention arm	Total nb 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

Table 1: Number of patients who will be included in the control and intervention arm for each of the eight investigating sites. 10 patients will be included per step.

Definition of study populations

- Total population: All participants included.
- Eligible population: All participants included without major violation of eligibility criteria.
- Intention to treat population: All patients will be included in the analysis in the group in which they were initially randomised and all their data will be used.
- Per protocol population: Only patients who are strictly compliant with the procedure will be included (Lost-of-follow-up will be, in particular, excluded).

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11.2. STATISTICAL ANALYSIS

11.2.1. Analysis strategy

An intention-to-treat analysis with replacement of missing data by multiple imputation will be performed as the principal analysis. To check the robustness of the results of the ITT analysis, sensitivity analysis will be performed.

A per protocol analysis on available data could be carried out a second time.

Descriptive analysis will always be presented overall and by treatment group.

Comparative analysis between procedure groups will be systematically performed. All comparisons will be performed with a type I error of 5%.

11.2.2. Statistical methods

Qualitative variables will be described by numbers and percentage.

Quantitative variables will be described by numbers, mean, standard deviation, median, range, and interquartile range.

We will attempt as much as possible to associate a graphic representation of the analyses.

Statistical analyses will be performed with the SAS® software (version 9.4) and R software according on the type of analysis.

11.2.3. Analysis plan

Description of the inclusions and follow up

The description of the number of inclusions per site and per step will be performed, globally and per group (before and after the implementation of the GerOnTe intervention).

Patients included in the analysis

Only the patients presenting at least one of the following conditions can be excluded from the analysis:

- patients wrongly included for unsigned consent,
- patients wrongly included for major non-respected eligibility criteria,
- patients who withdrew their informed consent.

The Trial Steering Committee (TSC) will make this decision of exclusion after documentation of observations by clinical trial statistical team at EUCLID, blinded to the procedure group and to the patient's evolution after inclusion.

Except for these exclusions, the patients who die, are lost to follow-up or leave the study, will all be included in the analysis.

Baseline characteristics

The following variables will be described:

- respect of the eligibility criteria,
- centres characteristics,
- patients clinical, socio-economic and socio-demographic characteristics.

Analysis of primary endpoint

The primary endpoint is the Quality of Life assessed by the EORTC QLQ-C30 (version 3.0) questionnaire at 6 months after GerOnTe implementation. It has 3 sub-scores that will be analyzed independently, with alpha risk adjustment.

In order to take into account the stepped wedge study design and its specificities (possible temporal effect, variable cluster size, presence of clusters), generalized mixed linear models will be used (Husset & Hughes 2007). Since the variables to be explained are quantitative (normalized scores), mixed linear regression models will be used. Random effects on the site, the time and the time of measurement (before/after the intervention is implemented) will be introduced where possible. The multiplicity of tests will be taken into account by adjusting the p-value using a Family-wise error rate method (Burman Stat Med 2009).

Analysis of secondary endpoints

- Quality of life assessed by the EORTC QLQ-C30 (version 3.0) and ELD 14.
 - The endpoints of quality of life will be analyzed in exactly the same approach as the primary endpoint.
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Survival
 - Depending on the event of interest, frailty models, nested frailty models or joint nested frailty models will be used.
- Patient autonomy assessed at 3, 6, 9 and 12 months:
 - By the Katz ADL questionnaire: the dependence score will be analyzed with a mixed linear regression model (with the same approach as the primary endpoint). A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
 - The proportion of patients living at home 6 months after inclusion will be analyzed with a mixed logistic regression model (with the same approach as the primary endpoint).
 - The number of completed chair stands in 30 seconds (Chair stand test) will be analyzed with a mixed linear or logistic regression model (with the same approach as the primary endpoint and depending on the distribution of the number of chair stands).
 - The frailty score and the grade of performance status (ECOG-PS) will be analyzed with a mixed logistic regression model (with the same approach as the primary endpoint).
 - Weight will be analyzed with a mixed logistic or linear regression model depending on the distribution of both variables (with the same approach as the primary endpoint).
- Patient anxiety assessed by the HADS at 3, 6, 9 and 12 months
 - These endpoints will be analyzed each with a mixed linear or logistic regression model depending on the distribution of the scores (with the same approach as the primary endpoint).
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Patient institutionalisation
 - The proportion of patients in nursing home at 6 and 12 months after inclusion will be analysed with a mixed logistic regression model (with the same approach as the primary endpoint).
- Unscheduled hospitalisations collected until 12 months
 - Depending on the event of interest, frailty models, nested frailty models or joint nested frailty models will be used.
- Cost-effectiveness and cost-utility analysis:
 - The economic evaluation will be conducted from a societal perspective, which accounts both the costs in the public payer perspective and other direct and indirect costs relevant for different stakeholders, including patients (e.g., transportation, formal and informal caregiver time and/or work leave, out-of-pocket expenses, or co-payments). A secondary analysis will

additionally be conducted from the payer perspective only, with the aim to estimate the budgetary impact on public finances. In this case, only the resource used within the hospital setting will be considered (e.g., direct medical costs, drugs and medications, bed-days, outpatient visits, ED visits).

- Costs will be calculated considering resource use at patient level and unit costs of each product/service used in the care pathway. Specifically, the process of calculating the full costs will be broken down into the following three connected tasks:
 - the collection of service usage data for individual patients over a defined period;
 - the costing or pricing of each service used; and
 - the combination of these two sets of information in order to calculate the cost of the full care packages

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 available sources. A map of available patient-level RWD (Real World Data) in each country will be created to generate real-world evidence.

Time spent will be measured by microcosting.

The full economic evaluation and any analyses of the study costs and outcomes will be carried out according to the “intention to treat” (ITT) 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 analyzed 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 analysis a standard discount rate of 3% per year will be applied to both healthcare costs and outcomes.

More details on the analysis plan for the economic evaluation in the protocol for economic evaluation:

- Caregiver burden assessed by the Zarit burden interview
 - This endpoint will be analyzed with a mixed linear regression model (with the same approach as the primary endpoint).
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Patient reported overall experience of person-centred coordinate care approach assessed by the P3CEQ at 6 and 12 months and qualitative analysis conducted by a health sociologist (see Ancillary study). This endpoint will be analyzed with a mixed logistic regression model since the variable are qualitative (with the same approach as the primary endpoint).
- Patient, physician and health-care-professionals-reported overall satisfaction and usability with the application of the GerOnTe intervention will be assessed by the MAUQ
 - Mixed linear regression models, allowing to take into account the centre effect but without taking into account the stepped wedge study design, will be used.
- GerOnTe patient-centred intervention implementation and usage
 - Mixed linear regression models, allowing to take into account the centre effect but without taking into account the stepped wedge study design, will be used.

12. RISK AND BENEFITS

There are no direct disadvantages or health risks associated with the participation of the patients in this clinical trial. The use of the digital application by itself does not cause any serious problems. Daily recording of symptoms can increase the focus strongly on these symptoms. This excessive attention can lead to increased anxiety. An increase in the number of unplanned hospital or GP visits is possible due to an alert in the digital application that is triggered by the reported symptoms.

In addition to the above mentioned risks, there is also a risk of technical problems with the digital application. More details on technical issues with Holis™ GV can be found in the document TD-Holis-5.2_Benefit risk ratio evaluation_v0.0_20220624.

Patients participating in this clinical trial are closely monitored by the medical team, consisting of at least an APN, geriatrician and oncologist. A tailored care pathway will be developed for the patient. With the help of technological support, changes in the patient's overall condition can be quickly detected and changes in the treatment plan can be proposed by health care professionals to the patient. During this tailored care pathway, the involvement of the patient in the treatment decision-making process will increase. Recommendations regarding the treatment plan will be made by the involved health care professionals. This will be discussed with the patient who is responsible for final treatment decision.

This clinical trial is conducted to evaluate the benefits of comprehensive care combined with a digital application compared to standard of care alone for your disease. This intervention will be considered as an advantage in clinical practice if it improves the quality of life of the trial participants.

13. MANAGEMENT OF ADVERSE EVENTS / SIDE EFFECTS / INCIDENTS

13.1. DEFINITIONS

The definitions and reporting requirements adopted in this protocol are based on the ISO 14155:2020 standard and according to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR) and Medical Device Coordination Group (MDCG) 2020-10/1.

13.1.1. Adverse Event (AE) (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

Note:

- This definition includes events related that are anticipated as well as unanticipated events.
- This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

13.1.2. User (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

Any healthcare professional or lay person who uses a device.

13.1.3. Serious Adverse Events (SAE) (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

A SAE is an adverse event that led to any of the following:

- Death,
- Serious deterioration in the health of the subject, that resulted in any of the following:
 - life-threatening illness or injury,
 - permanent impairment of a body structure or a body function,
 - hospitalisation or prolongation of patient hospitalisation,
 - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - chronic disease,
- Foetal distress, foetal death or a congenital physical or mental impairment or birth defect

13.1.4. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

13.1.5. Device Deficiency (DD)

A DD is an inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

13.1.6. Unanticipated Serious Adverse Device Effect (USADE)

An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered as Serious Adverse Device Effects. A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

13.1.7. SERIOUS PUBLIC HEALTH THREAT (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

13.1.8. SEVERITY GRADE

Severity grade for adverse events will be based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Grade 1: the degree / extent / intensity of the event is mild (no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)

Grade 2: the degree / extent / intensity of the event is moderate (minimal intervention; local intervention; noninvasive intervention)

Grade 3: the degree / extent / intensity of the event is severe and undesirable (significant symptoms requiring hospitalisation or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: the degree / extent / intensity of the event is life-threatening or disabling

Grade 5: Death related to Adverse Event.

13.1.9. CAUSALITY ASSESSMENT

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

13.2. INVESTIGATOR'S RESPONSIBILITIES IN CASE OF ADVERSE EVENT / SERIOUS ADVERSE EVENT / DEVICE DEFICIENCY / NEW INFORMATION AND OTHER EVENTS

Upon signing the consent form, the investigator is responsible for collecting all adverse events and device deficiencies. He reports all serious and non-serious adverse events as well as device deficiencies that could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favorable, occurring during the use of the Holis Dashboard or the Holis Patient App. For example: wrong information provided to the patient (Holis Patient App).

The reporting period is defined as follows:

- From the date of signing the consent,
- For the duration of the patient's planned follow-up in the research,
- Until 30 days after the end of the participant's follow-up planned by the research, when it is likely to be due to the research.

The investigator reports any inadequacy in the identity, quality, durability, reliability, safety or performance of the investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer, in the SAE and Device deficiency case report form.

As the TWOBE study is a streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management, no research-related AE and SAEs are expected.

The following situations should not be reported immediately to the sponsor but should be reported and documented by the investigator in the CRF:

- All non-research related events (i.e., disease progression, death...),
- Any admission for social or administrative reasons, in the absence of an adverse event,
- Any hospitalisation for medical or surgical treatment scheduled before the research; any pre-planned surgery or medical treatment must be recorded in the patient file.

AE and SAE related to cancer treatments should not be reported.

13.2.1. NOTIFICATION WITHOUT DELAY OF SERIOUS ADVERSE EVENTS AND, DEVICE DEFICIENCY AND NEW INFORMATION

The investigator assesses each adverse event in terms of its severity and each device deficiency in terms of its potential to result in an SAE if appropriate measures or intervention were not taken, or if the circumstances were less favorable.

The investigator shall notify any SAE or device deficiency that might have led to a serious adverse event to the sponsor, immediately, and **no more than 3 calendar days** from the day he/she becomes aware of it, occurring:

- from the date of signing the consent,
- during the entire duration of the patient's follow-up under the clinical investigation,
- until 30 days after the end of the participant's follow-up planned by the clinical investigation,
- using the AE/SAE form for notification of the study team to the sponsor (appendix 13).
- using the DD form for notification of the study team to the sponsor (appendix 14).
- using the SAE/DD form for notification of the sponsor to the CA's¹.

If an authorized investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the sponsor by a health care professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

If the investigator becomes aware of a serious adverse event, suspected to be causally related to the clinical investigation, occurring after the end of the clinical trial, he will inform the sponsor without delay.

¹ The SAE report form in excel format can be downloaded from the following web page:
https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

13.2.2. Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). The sponsor will notify all deaths as soon as possible after becoming aware to the EC and provide additional information if requested.

13.3. DECLARATION BY THE SPONSOR OF SERIOUS ADVERSE REACTIONS, DEVICE DEFICIENCY, NEW INFORMATION AND OTHER EVENTS

The investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the sponsor in accordance with instructions provided above.

The sponsor will promptly evaluate all SAEs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to investigators, ECs and applicable CA's based on applicable legislation.

13.3.1. Sponsor's reporting of Serious Adverse Events and Device Deficiencies

In accordance with article 80 (2) Regulation (EU) 2017/745 – Medical device regulation, the sponsor shall declare (via EUDAMED as soon as it is fully functional or via the Medical Device Coordination Group (MDCG) Report Form: MDCG 2020-10/2 Clinical Investigation Summary Safety Report Form v1.0) to all the national competent authorities where the clinical investigation is authorised to start:

1. Any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
 2. Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
 3. Any new findings in relation to any event referred to in points 1 and 2.
- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes deaths. Follow-up: Immediately, but not later than 2 calendar days after awareness by sponsor
 - Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event. Follow-up: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor.

The sponsor shall declare any new information that arises during the research to the CA's of participating countries and to Ethics Committee(s) when applicable, as required by European regulation.

The sponsor and the investigator shall take the appropriate urgent measures.

13.3.2. Annual reporting

The Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's and CA's containing an overview of all SAEs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

13.3.3. Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	Non-serious AE	e-CRF	Sponsor	NA
	SAE/DD	Initial SAE/DD form + follow up if necessary	Sponsor	Asap, but no later than 3 calendar days after awareness
	Death	SAE form	Sponsor	Asap
	New information	Written report	Sponsor	Asap
Sponsor	All reportable events (of all participating sites)	EU SAE report form (excel) ²	<ul style="list-style-type: none"> CA for Belgium - > FAGG: via mail to ct.rd@fagg.be CA's other participating countries PI's of participating sites 	Asap, but no later than: <ul style="list-style-type: none"> 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) 7 calendar days (all other reportable events)
	Death	SAE form + narrative	Ethics Committees	Asap
	Annual Progress Report	APR template	<ul style="list-style-type: none"> Ethics Committees CA for Belgium - > FAGG : via CESP portal CA's other participating countries 	Annually

² The SAE report form in excel format can be downloaded from the following web page:
https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

14. QUALITY ASSURANCE AND TRIAL MONITORING

14.1. MONITORING OF THE TRIAL

14.1.1. Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Prof. P. Soubeyran, Coordinating Investigator FRONE and Chairman of the Committee,
- Prof. H. Wildiers, Coordinating Investigator TWOBE and co-chairman of the Committee,
- Principal investigator the Netherlands, geriatric expert (M. Hamaker or a substitute),
- A representative of the sponsor (C. Kenis or a substitute),
- A representative of EUCLID (C. Schwimmer or a substitute)
- The biostatistician of the trial (M. Kret, or a substitute),
- The Methodologist (F. Saillour-Glenisson, or a substitute),
- The coordinating Clinical research manager (C. Duchiron, or a substitute).
- An independent geriatrician (S. Festen, or a substitute)
- An independent oncologist (N. Battisti, or a substitute)
- An independent statistician (F. Canoui-Poitaine, or a substitute)

This committee must ensure the following:

- **Review of the protocol before submission,**
- Implementation and regular follow-up of the study,
- Participant protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated, and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

14.2. QUALITY ASSURANCE

14.2.1. Data collection

Quality of life and various questionnaires will be collected in the same way in both arms through paper questionnaires by study collaborators.

The data will be collected on an electronic case report form (eCRF) and directly input via the Internet. Only the study collaborators appointed by the sponsor and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by an online trial management software on the Internet (Macro v4, Informed Company); it will be transferred and monitored remotely in real time.

The study collaborator appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study collaborator will contact the investigators regarding the study implementation visit.

All of the necessary data will be collected on an electronic case report form (eCRF) provided by the sponsor. The generic names of medication will be given in Dutch.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The investigator or the study collaborator at the authorized centre will validate the case report form whenever data is entered.

14.2.2. Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the KU Leuven/UZ Leuven,
- the quality control of the research site data by a clinical research assistant (CRA) whose role is to:
 - check compliance with the protocol, GCP and current legislation and regulations,
 - check the consent and eligibility of each participant taking part in the trial,
 - check the consistency and coherence of case report form data against the source documents.
 - check that each serious adverse event is reported,
 - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the participants have not participated in a trial for which an exclusion period currently applies.
- The possible audit of study centres,
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form (eCRF) and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each participant (100% level): participant identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, principal response variables. The personal data relating to each participant shall remain confidential. On the electronic case report form (eCRF) or any other form dispatched, the participants will be identified solely by an inclusion

number composed of numbers and letters. However, the investigators must keep a list identifying the participants in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant data required strictly in accordance with this control procedure. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each participant in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

14.2.3. Handling of missing data

The monitoring of data will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

14.2.4. Audits

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit. All the documents relating to this study must be available for such an inspection after prior notification.

14.2.5. Data management

The data are entered using an electronic case report form (eCRF) created with Macro 4 (Infermed limited 2010). Data entry is performed by the study collaborator on site using login and password provided by the database administrator. It is carried out at the KU Leuven/UZ Leuven.

Each step of the data management is described in the data management plan (DMP) drafted by the data manager. This document is validated by the coordinating investigator, the statistician, the CRA and the database administrator and is performed according to the internal procedures of the research unit.

The process of data lock/unlock is performed according to our procedure and after validating a check list.

All data will be backed-up daily and kept for 30 days.

15. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

15.1. ETHICS COMMITTEE (EC) REVIEW AND REPORTS

Before the start of the trial, this protocol and other related documents (e.g. informed consent forms, investigator's brochure, etc.) will be submitted for review to the Ethics Committee and to the relevant competent authority for trial authorization. The trial shall not commence until such approvals have been obtained and until other relevant essential trial documents, such as duly signed contract agreements, are in place.

It is the responsibility of the coordinating investigator to produce the Annual Progress Report (APR) and submit to the Ethics Committee/competent authority within 30 days of the anniversary date on which favourable opinion to start the trial was given, and annually until the trial is declared ended.

The coordinating investigator shall notify the Ethics Committee/competent authority of the end of the trial. In accordance with MDR article 77 study end reporting is mandatory within 15 days (but 24 hours if based on safety grounds). The coordinating investigator will submit a final report with the results of the study, including any publications/abstracts, to the Ethics Committee/competent authority within 1 year of trial termination or within 6 months for paediatric trials.

15.2. REGULATORY COMPLIANCE

15.2.1. For Belgium

The trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in Directive 2001/20/EC or EU Regulation 536/2014 or the Regulation (EU) 2017/745 of 5 April 2017 on medical devices, as applicable, and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use or the Belgian law of December 20nd 2020 on medical devices, as applicable, and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

15.2.2. For the Netherlands

The trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in the Good Clinical Practice (decision of 24 November 2006), the Dutch law regarding medical research involving human subjects (WMO), the EU General Data Protection Regulation 2016/679 (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (AVG).

15.3. PROTOCOL / GCP COMPLIANCE

The trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the trial data are credible, reliable and reproducible.

The investigator and trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the coordinating investigator and sponsor. Deviations should also be reported to the Ethics Committee and/or competent authority as part of the EC's continued review of the trial (e.g. through the annual safety report, annual progress report, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the trial participants; or
- the scientific validity of the trial

The investigator is expected to take any immediate action required to protect the safety of any participant included in the trial, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the Ethics Committee and/or competent authority at the trial site should be informed according to local procedures and regulations.

15.4. DATA PROTECTION AND PARTICIPANT CONFIDENTIALITY

The trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian and Dutch laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data and the Dutch law of May 25th 2018 regarding data protection (AVG). Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws. In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR.

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

15.5. INSURANCE POLICY

15.5.1. For Belgian participating sites

Art. 32 of the Belgian Law of December 20nd 2020 on medical devices applies.

Prior to the start of the trial, the sponsor shall enter into an insurance contract in order to adequately cover trial participants from Belgian sites in accordance with art. 32 of the said law.

The KU Leuven/UZ Leuven has obtained an insurance policy (Amlin Insurance SE- Policy number 299.053.700 – Vanbreda Risks & Benefits NV, Plantin en Moretuslei 297, 2140 Antwerpen, Belgium) in case compensation is payable to investigators or participants taking part in the study.

15.5.2. For Dutch participating sites

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Stichting Diaconessenhuis Utrecht has obtained a liability insurance (Policy number 624.100.016 – Onderlinge Waarborgmaatschappij Centramed B.A., Maria Montessorilaan 9, 2719 DB Zoetermeer, the Netherlands) in case compensation is payable to investigators or participants taking part in the study.

15.6. AMENDMENTS

If a substantial amendment to the clinical trial agreement or the documents that supported the original application for the clinical trial authorisation is needed, the sponsor must submit a valid substantial amendment to the Competent Authority (CA) for consideration, and to the Ethics Committee for review and approval. Substantial modifications to the clinical investigation must be approved by both the FAMHP and EC before their implementation. The content of the submission package for substantial modifications includes a European application form for substantial modifications. This form will be accompanied by a cover letter with a brief description of the substantial modifications, a list of documents submitted with a clear indication of which documents have been updated/added and the necessary documents that provide a clear overview of the modifications. FAMHP and EC will provide one consolidated decision in accordance with timelines defined by applicable regulations. It is the sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the CA and/or EC.

15.7. INFORMING AND OBTAINING CONSENT FROM PARTICIPANTS

Prior to carrying out medical research on human participants, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the study collaborator and after sufficient time for reflection has been allowed.

The study collaborator in charge of the participant will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The participant can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The participant's written consent will be obtained prior to entry into the study by using the Participant Information Sheet and Informed Consent Form. These forms must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the study collaborator. The original will be given to the participant and the second, archived in the study collaborators folder. Upon request, a copy will be sent to the sponsor in a sealed envelope.

15.8. SPONSOR'S RESPONSIBILITIES

The sponsor of the clinical trial, the KU Leuven/UZ Leuven, will take the initiative for this clinical trial. The KU Leuven/UZ Leuven will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain clinical trial approval for the initial project and any amendments through a consolidated opinion of FAMHP and EC,
- Give trial-related information to the site directors and investigators,
- Notify the relevant authority of the trial start and end dates,
- Draft the final trial report and sent the summary to FAMHP,
- Send the trial results to the relevant authority, EC and investigators,
- Archive essential trial documents in the sponsor's folder for a minimum period of 25 years after the trial has ended.

15.9. INVESTIGATORS' RESPONSIBILITIES

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved through a consolidated approval by both the FAMHP and the Ethics Committee.

The investigator must not make any changes to the protocol without the written consent of the sponsor or without both the FAMHP and the Ethics Committee having authorized the proposed changes through a consolidated decision.

It is the responsibility of the principal investigator:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start participant enrollment after authorisation has been obtained from the sponsor,

- to ensure that he/she is available for investigator's meeting and for "monitoring".

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs or eCRFs) for each of the participants enrolled in the trial and to allow the Clinical Research Assistant (CRA) duly authorised by the Sponsor a direct access to source documents so that the latter can validate the data on the CRF or eCRF,
- to date, correct and validate corrections on the case report forms (CRFs or eCRFs) and the Data Query Forms (DQFs),
- to accept regular visits of the CRA and eventually visits of auditors duly authorised by the Sponsor or inspectors of regulatory authorities,
- to inform trial participants of the overall results of the research on first demand.

15.10. AUTHORITY TO EXECUTE THE TRIAL

The investigator shall certify that he/she is authorised to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other agreements that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

15.11. DATA PROCESSING

The data recorded during this research are the subject of a computerised processing on behalf of the sponsor (KU Leuven/UZ Leuven) in accordance with the EU General Data Protection Regulation 2016/679 (GDPR) and relevant Belgian and Dutch national laws implementing the GDPR.

Furthermore, if the biomedical research data is computer processed or managed by computerised systems, each centre:

- shall check and document the fact that the computerised systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation),
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems,
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail),
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access,
- shall update the list of persons authorized to amend the data,
- shall keep appropriate back-up copies of the data,
- shall maintain blind status, where applicable (e.g. during data entry and processing).

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify participants taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these participants to be identified whilst maintaining the confidentiality of the personal data.

The archiving data is performed according to the applicable regulations and under the responsibility of investigator. All data and the participant identification codes will be kept for at least 25 years after the completion or discontinuation of the trial.

16. CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained, and the data and results generated by the trial legally belong to as their obtaining the KU Leuven/UZ Leuven, which can use this data at its own discretion.

According to applicable laws and regulations regarding personal data protection and the processing of personal data, investigators and people who will have to collaborate in the trial shall be bound by professional secrecy with regard to the particular nature of the products studied, trial, trial participants, and results. In particular, all documentation relating to the trial sent to the investigator should be considered confidential information.

Without the consent of the sponsor, the investigator cannot give information about trials to anyone, except the Minister in charge of Public Health, public health medical inspectors, public health pharmacists inspectors, the General Director and inspectors of FAMHP.

The trial cannot be the participant of any written or verbal comments without the sponsor's consent.

17. PUBLICATION AND VALORISATION

17.1. RESEARCH REGISTRATION

The declaration of Helsinki (latest version) and European, Belgian and Dutch regulations require that every research trial involving human participants be registered in a publicly accessible database before recruitment of the first participant.

17.2. SCIENTIFIC COMMUNICATION

All of the information arising from this study shall be considered confidential.

All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities) and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required. In any case, the sponsor will control the first publication.

Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the KU Leuven/UZ Leuven, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial and listing any organizations that have provided financial support.

For the principal publication, either in Dutch, French or English, the authors are:

- the study coordinator
- the investigators will be listed on a pro rata basis according to the number of participants recruited
- persons deeply involved in the trial design and performance
- a representative of the trial statistics unit (in the first 3 positions or two last positions according to degree of involvement in the preparation of publications)

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APPENDIX 1: GERONTE – PROTOCOL FOR PRE- AND POST-IMPLEMENTATION EVALUATION AT CLINICAL TRIAL SITES

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1. BACKGROUND AND RATIONALE

GerOnTe is a 5-year research and innovation project (April 2021 to March 2026) funded by the European Union within the framework of the H2020 Research and Innovation programme, in response to the health societal challenge topic SC1-BHC-24-2020 “Healthcare interventions for the management of the elderly multimorbid patient”. The overall aim of GerOnTe is to improve quality of life - defined as well-being on three levels: global health status, physical functioning, and social functioning- for older multimorbid patients, while reducing overall costs of care. To this end, GerOnTe will co-design, test, and prepare for deployment an innovative cost-effective patient-centred holistic health management system (GerOnTe intervention).

GerOnTe intervention will test the feasibility of integrating the care provided by cancer and other morbidity healthcare professionals into a novel care pathway that is coordinated by an Advanced Practice Nurse (APN) as the case manager. The integration of health professional and patient data will enable shared and improved decision-making and patient-centred personalised care. The intervention will establish; 1. a Health Professional Consortium (HPC), by integrating and coordinating the relevant healthcare professionals; and 2. the processes, the health data (medical, and patient self-reports), and the communication networks and sequence needed to facilitate patient-centred decision-making for patient with cancer and other morbidities. GerOnTe will also aim to design a complimentary application (Holis Patient Application) that will systematise and improve the efficiency of decision-making through the sharing of health and personal data in a secure way.

The GerOnTe intervention will address three important issues experienced in the healthcare system. It will co-create an intervention that is co-designed by stakeholders to work with the **existing systems in place**. GerOnTe will be accompanied by an EU wide implementation guide that provides sufficient detail (of the mechanism of action, the critical and supportive components, and influencing contextual factors) to enable adaption to local setting. GerOnTe will offer a feasible and practical way to bridge the elusive gap between disease-focused model of care and patient-focused models of care (without disintegration of the current models of care that are deeply embedded in current practice and offer many benefits (specialist care themselves). The GerOnTe intervention is an impactful intervention that is expected to offer similar benefits to other population of patient and healthcare providers needing a practical way to build a patient-centred approach into existing systems. The GerOnTe intervention will offer a practical and pivotal solution to the current fragmented system of care, to a more integrated and coordinated care.

The GerOnTe intervention facilitates achieving the triple aim (Berwick, Nolan, and Whittington 2008) to improve quality of life, improve experience of care and reduce costs.

The GerOnTe intervention, therefore, is more than just implementing technology and an Information Communication Technology (ICT) Tool, it is a complete transformational undertaking that impacts an organisation’s people, change management processes, and current and future business models.

Since healthcare system configuration varies from one country to the other and has a strong impact on the delivery of care and on patient health status, an important part of the GerOnTe project is to take into account the context and the organization of healthcare services. This is particularly true for multimorbid patients who often meet several professions, require multiple services, and span different setting and providers. Indeed, the management of older people with multiple conditions challenges usual care delivery, which is frequently structured around pathways of care for single diseases.

A comprehensive and detailed assessment of the clinical trial sites is needed to support successful implementation, scale-up, spread and sustainability, of the GerOnTe intervention and to allow, scientifically robust reporting and dissemination. This will require a significant amount of coordinated, pre-planned but flexible ground work to capture the required scope and depth of accurate data while minimising the burden on local sites and services. This assessment will provide a baseline for a business, economic and implementation evaluation of inputs, context, processes, and outputs.

An essential aspect of the business, economic and implementation evaluation that will be run as part of WP3 and WP5 will be having a good understanding of the baseline processes with a well-developed conceptual model, of how the solution is expected to work (Pawson and Tilley 1997).

2. OBJECTIVES

GENERAL OBJECTIVE

The primary objective of this ancillary study is to inform and support the economic and realistic evaluation, and the GerOnTe Business Plan to support wider EU dissemination of the GerOnTe model. A critical and time-sensitive aspect of this ancillary study is the identification and collection of all relevant data to enable meaningful analysis and documentation to support robust empirical reporting and analysis.

SPECIFIC OBJECTIVES

The specific objectives of this study are to:

1. identify, describe, analyse, and map the common and distinctive elements and gaps of the current care pathways for older multimorbid patients with cancer as a dominant morbidity within each clinical sites involved, including the preparation of process maps showing the initial state of the care pathway (Kononwech et al 2020).
2. document and analyse the process of implementation of the intervention in the trial sites beyond the specific trial outcomes to enable analysis of the mechanism of action of the intervention, the contextual factors and barriers and facilitators to implementation and application of the GerOnTe intervention (to develop a comprehensive implementation guide that will inform implementation across diverse settings).
3. evaluate the impact of the GerOnTe intervention on the evolution of practices and organizations at hospitals and build recommendations for its deployment in other contexts.

3. ELIGIBILITY CRITERIA

Each clinical site participating in the trial will be involved in the ancillary study.

In each clinical site, the principal investigator (PI) will identify and recruit relevant staff members (e.g., physicians, nurses, clinical and financial managers, IT and administrative staff), and a small selection of patients/family members/carers following a stakeholder analysis approach (Brugha and Varvasovszky, 2000). Therefore all the relevant stakeholders who can inform the understanding of the behaviours, intentions, agendas, interests, interrelations, and the influence or resources that will impact the intervention and its implementation will be identified, recruited, and involved. The PI will provide the research team with the comprehensive list of relevant stakeholders to be interviewed for the purposes of the Ancillary study.

This data will be used to inform and support successfully:

1. Evaluation of the current and post-GerOnTe implemented care pathways in each clinical trial site;
2. Implementation of the intervention at each clinical trial site;

3. Deliverables on the business, economic, and implementation evaluations.

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4. SAMPLE SIZE AND METHOD

A baseline assessment will involve a number of qualitative methods (e.g., questionnaires, semi-structured interviews and focus groups) with the relevant stakeholders. The choice between questionnaires, individual interviews and focus groups (FG), and between end-user specific (such as patient only FG) and mixed FG (such as clinicians and patients) will be determined by the FG / interview aim, stage of the assessment (pre, during or post trial), and the practical factors such as participants' availability and preferences. However, the ancillary study will aim to organise and support mixing and collaboration between stakeholders in line with the GerOnTe's broader end-user focused and collaborative approach.

The relevant stakeholders to involve will be selected with the support of the principal investigator in each clinical site. The number of participants included will depend upon the number required to inform all important elements of the phenomenon being studied (when data saturation is achieved). We expect that approximately 3-5 staff members and 5-10 patients and/or family members/carers (from both the intervention and the control arm) will be involved in each site over the entire duration of the project resulting in a total of approximately 20-30 staff members and 40-60 patients across all sites). The sample size will be evidenced as sufficient when additional interviews or focus groups do not result in emergence of new concepts. This inductive approach allows us to document the emergence of new themes and also to identify perspectives that may otherwise be overlooked (Sargeant 2012).

5. OUTCOMES

The outcome of the study will be:

1. A map of the current care pathways, people, formal and informal processes, and technology, and a descriptive analysis of the current care pathway for older multimorbid patients with cancer as dominant morbidity, in each clinical site. This will represent the pre-GerOnTe context for each site.
2. A descriptive analysis that identifies the (GerOnTe) mechanism of action, and the contextual factors that can act as barriers or facilitators to the intervention or its implementation, with an accompanying guidance document that supports widespread implementation of GerOnTe.

6. ANCILLARY PROCEDURES

Data will be collected, using both qualitative and quantitative approaches, including interviews, focus groups, questionnaires, direct observation, and document review.

The relevant document to inform the implementation, economic and business case reports will be identified in collaboration with the trail site PI or their designated person. Key documents will include the organisation's formal policies and reports related to clinical and business practice, processes, standards, and outcomes, minutes of relevant meetings, and documentation from multidisciplinary team (MDT)/health professional consortium (HPC) meetings. Neither patient nor clinical details will be sought, accessed, nor recorded, as this is purely a review of MDT processes.

The intents are:

1. to document the care pathways and the consumption patterns of multimorbid older patients with cancer as dominant morbidity before and after the introduction of GerOnTe. The care pathways will be analysed according to the various phases of the care process: noticing the symptoms and first detection, assessment and diagnosis, treatment and care service definition, and service delivery and follow-up.

2. to collect data on:

- the contexts and implementation processes at each trial site,
- Patients, physician and health professional experience with Holis Patient App and with GerOnTe,
- Individual and collective barriers and facilitators to GerOnTe intervention implementation and usage,
- The impact of the GerOnTe intervention on the evolution of practices and organizations at hospital level, for health professionals.

This work will be done in the relevant local languages, with fieldwork conducted by the research team.

In each clinical site participating in the trial, we will follow the undermentioned flow (figure 5) and procedures (for the Principal investigator and the involved researchers).

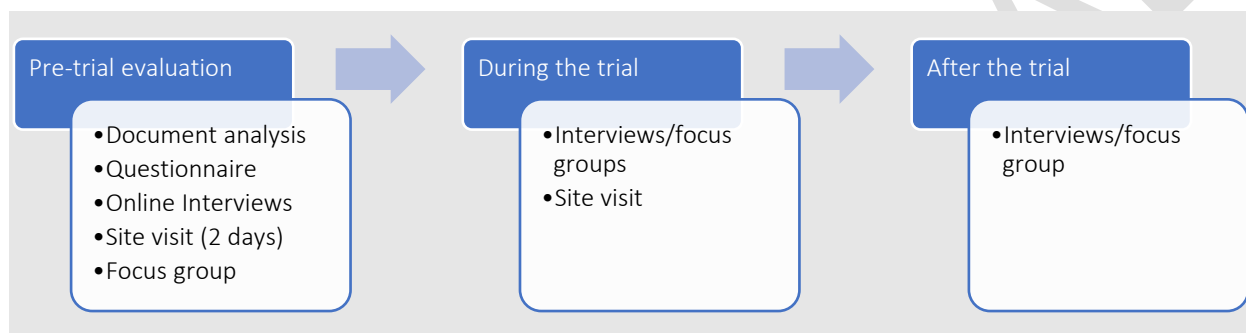


Figure 5

Procedure for the Principal investigator

For each site, before the trial starts the PI:

- Will make sure to identify and share with the research team relevant document about the clinical site (e.g., organisation policies, reports, etc.),
- Will make sure that the identified stakeholders complete a questionnaire that will be sent to them,
- Will make available the identified stakeholders for Zoom interviews (or other similar teleconference technologies),
- Will support the scheduling and organization of on-site visits of the research team.

For each site, during the trial, the PI:

- Will make sure that the identified stakeholders participate in the follow-up interviews and focus groups,
- Will support the scheduling and organization of on-site visits of the research team.

Procedure for the researcher

BEFORE THE INTERVIEW

- Explain the objective of the interview to the relevant stakeholders (e.g., physicians, nurse, clinical and financial managers, IT and administrative staff), identified by the site principal investigator,
- Obtain agreement to an interview.

DURING THE INTERVIEW

- Collect informed written consent,
- Carry out an interview, collecting data as described below, and arranging for it to be recorded, if the participant(s) agree, and transcribed for further analysis (in line with GDPR and local ethics requirements),
- Identify from the interviews key documents, arrange access to these, and review them.

AFTER THE INTERVIEW

- Summarize the collected information and analyse them,
- Prepare a report on the initial state and final state for each centre in a manner and level of detail that enables achievement of the outcomes set out above,
- Share the relevant analysis with Partners involved in the trial to enable implementation of the intervention at individual trial sites in a way that considers the differences (that may impact the intervention success),
- use the information collected to inform the business, economic and implementation evaluation, and guidance documentation.

6.1 Questionnaires

Introduction: The aim of the questionnaire is to collect data on the organizational model of the site participating in the project and in particular the delivery and service model before conducting an interview. The focus is on older people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

6.1.1 For Clinical site Principal investigator

The questionnaire will cover these domains:

- Volumes of activities and patient characteristics (e.g., how many patients are treated by the centre, age group, needs) (*Patient volume planning and control*),
- Long-term policy of the institution (*strategic planning*),
- Institutional engagement, experience, or policy document supporting change management,
- Operational strategy, in terms of available professionals, equipment and space (*resource planning and control*),
- Multidisciplinary models (e.g. MDT),
- Institutional funding model (public/ private/ mixed), and service type and use by proportion of public/ private patients (if mixed),
- Relevant recent or current service or innovation changes or improvement taking place,
- Patient engagement and feedback procedures,
- Staff recruiting, training, development, and retention and service development practices,
- Professional representation and decision-making around service delivery,
- Patient representation and decision-making around service delivery.

6.1.2 For Clinical trial site staff (clinicians, and clinical, business, technology managerial staff):

The questionnaire will cover these domains:

- Employment experience related to GerOnTe (complex) patient population,
- Experience with integrated care at existing or previous work,
- Experience, views, and awareness of their organisation's policies and supports around change management,
- Previous experience and views around implementing complex or technology in their clinical setting,
- Experience and views around potential challenges, competitors and facilitators to implementing complex technology change in their setting.

6.2 Semi-structured interview

Introduction: The aim of the interviews is to describe the organizational model of the site participating in the project and in particular the delivery and service model. We're especially interested in people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

6.2.1 For Clinical site Principal investigator (for all 8 participating sites)

BEFORE IMPLEMENTATION OF GERONTE INTERVENTION

- Can you explain the long-term policy of the institution (*strategic planning*)?
- Can you explain the organizational model of the site?
 - Describe core and peripheral contents of the service offered by the centre.
 - Patient access points, process standardization, interaction methods with patients and families
 - Services dedicated to taking charge of the patient (e.g., physical location, organizational dependence, dedicated clinics, specialization)
- Can you describe how older people with cancer and other complex health needs are cared for right now – is there a formal care pathway, or how is it done? (*Patient planning and protocol*)
 - Description of the care pathway in the different phases: sending, diagnosis, treatment and follow up
 - Who is involved? What do they do? When? Where? Why?
- How do you interact with other professionals / specialties and nodes of the network (e.g., GP, other professionals, facilities, other units)?
- Do you have regular team meetings – multi-disciplinary team meetings? For which patients? How do these meetings work?
- What difficulties do you currently face in the management of older multimorbid patients?
- What work, or informal practices do you do, or try to do, to fix problems or delays in the system? How do you typically access and share information about your patients?

AFTER INTRODUCTION OF GERONTE INTERVENTION

- Speaking of the GerOnTe pathway, what did you have to do to make it happen in your service?
- What did other people have to do?
- From your point of view, is it working well in your service?
- What would you like to change to improve it or make it work better?
- What helped you bringing in this new pathway?
- What got in the way of bringing in the new pathway?
- Specifically, how is the new technology working for you and your colleagues?
- Does this technology impact (in a good or bad way) on any other technology you use or work you do?
- How do you think the technology is going for other colleagues, and for patients and their families?
- Overall, do you feel GerOnTe has affected your work – has it been a good experience or a bad experience? What were the benefits, and the costs, of GerOnTe from your perspective?
- Do you think GerOnTe will continue to be used on your service when the study is over?

6.2.1 FOR STAFF MEMBERS (HPC)

BEFORE IMPLEMENTATION OF GERONTE INTERVENTION

Introduction: We'd like to talk a bit with you about how care is delivered to older people with cancer in your service. We're especially interested in people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

- Can you describe how older people with cancer and other complex health needs are cared for right now – is there a formal care pathway, or how is it done?
 - Description of the care pathway in the different phases: sending, diagnosis, treatment and follow up
 - Who is involved? What do they do? When? Where? Why?
 - Do patients need to initiate or follow up on much of the care?
 - Do you think certain groups are disadvantaged and how?
- What makes care work well? What makes care doesn't work well?
- What gets in the way of delivering the care you would like to give?
- What would you like to see that you haven't yet have?
- Do you have regular team meetings – multi-disciplinary team meetings? How do these meetings work?
- How do you typically access and share information about your patients?
- What would improve this communication process?
- How do you interact with other professionals and nodes of the network (e.g., GP, other professionals, facilities, other units)?

INTRODUCTION OF GERONTE

- How are you involved in bringing in this new care pathway?
- What do you think it should achieve to be useful?
- Do you see challenges to bringing in this care pathway? And what do you expect it will achieve?
(plus follow on of why do you think it will achieve this [lesser goal])
- How was/will it be brought into use in your service?

AFTER INTRODUCTION OF GERONTE INTERVENTION

- Speaking of the GerOnTe intervention, what did you have to do to make it happen in your service?
- What support/ information/ teaching did you get on GerOnTe, your role in GerOnTe, and how GerOnTe should be implemented?
- What did other people have to do?
- From your point of view, is it working well in your service?
- What helped you bringing in this new pathway?
- What got in the way of bringing in the new pathway?
- Specifically, how is the new technology going for you and your colleagues?
- How do you think the technology is going for other colleagues, and for patients and their families?
- Overall, do you feel GerOnTe has affected your work – has it been a good experience or a bad experience? What were the benefits, and the costs, of GerOnTe from your perspective?
- Do you think GerOnTe will continue to be used on your service when the study is over?
- If GerOnTe was staying, what would you change about it?

6.2.2 PATIENTS, FAMILY, AND CAREGIVERS

INTRODUCTION:

We're looking at how care is given to older people like you (your relative) with cancer in this hospital. We're trying to understand how care is done and get some understanding of how this affects you. We're especially interested in how information about you, and about how you are doing, is shared with you and with your doctors, nurses, and other health care professionals.

- How are you finding the care you get here all-in-all?
- Do the people you meet know what you expect them to know about, you, about your treatment, and about your progress?
- Do you find yourself having to tell the same things to different people, or do you feel that they are sharing what you've told them about you?
- Do you know, more or less, what's happening with your treatment?

- Who would you go to if there was a problem, you thought might be related to your treatment?
- Who would you go to for a problem, maybe with a condition you already have, that isn't related to your treatment?
- What has helped you most in your care journey?

For patients using the GerOnTe Patient App:

- What is your general opinion about using the app?
- How is it useful to you?
- What else would be helpful to you?
- What encourages you to use it?
- What puts you off using it?

FOR PATIENTS NOT USING THE GERONTE PATIENT APP

- How do you see yourself using an app?
- Would you find it useful to you?
- What would encourage you to use it?
- What would put you off using it?

7. RECRUITMENT AND CONSENT

All participants involved in the study will sign an interview informed consent form (hereafter referred to as 'Form'). The form will collect the following information:

1. Confidential Personal Data (as defined by the GDPR, 2018) such as – Name of interviewee, age, gender, grade, and specific role of participant, and date of interview. This will be managed in line with GDPR (2018), local ethical requirements, and participants' wishes.
2. Open information:
 - Site
 - General role (e.g., patient, oncologist, nurse, ...)
 - Description of interview setting – one-on-one, team interview (focus group)

Moreover, the Form will include a brief description of the project, the terms, and conditions of being a participant, a signature from the researcher and from the participant.

8. DATA MANAGEMENT

The purpose of data collection will be to gather the necessary information:

1. relating to the context of each site,
2. relating to the implementation of GerOnTe intervention in each clinical site,
3. to develop a robust economic evaluation that support the broader and complex value of the GerOnTe intervention,

4. To develop an empirically based Business Plan to support widespread dissemination of the GerOnTe intervention.

Data will be managed and disseminated in line with GDPR (2018), the GERONTE Data Management Plan and section §4.6.1 and 4.6.2 of the GerOnTe consortium agreement signed by all beneficiary partners.

The Data recorded during this research will be collected, stored and analysed in accordance with the Data Protection Laws. Each Party involved will provide adequate measures to ensure Data protection and, confidentiality regarding local, national, and international rules on data protection. The data collected will be stored in selectively accessible folder, anonymized and functionally separated. Each step of the data management is described in the data management plan (DMP) drafted by the data manager.

9. STATISTICAL AND DATA ANALYSIS

Given the complexity of the study, the analysis will adopt both a deductive and inductive approach.

A mixed inductive-deductive approach will be used to map the patient journey within each clinical site before the implementation using data collected from interview and document review. The researcher will collect data relevant to analyse the context (Phase 1 – Gather data), and once a substantial amount of data have been collected, we will look for patterns in the data (Phase 2 – analysis), working to develop a theory that could explain those patterns (Phase 3 – Develop Theory).

The implementation evaluation will use a more deductive approach and will use evidenced-based Implementation Science theory and framework to guide the data collection, analysis, synthesis, and development of an EU wide Implementation Guide (D5.4) and GerOnTe [Guide] to Implementation and Challenges D5.2. The implementation evaluation will also be sensitive to, and will be shaped and informed, inductively to ensure an implementation evaluation and guide that captures the broad and complex scope of the GerOnTe intervention. Interview, questionnaire, document review and observation (of non patient-care) processes will be analysed in line with the relevant qualitative and quantitative relevant evidenced-based techniques.

Development of the Business Case will involve close collaboration with relevant Partners to support and guide identification of the type and depth of data to be collected to support the development of a Business Case that representative of GerOnTe's scope and aim. The relevant data will be identified, collected, and analysed. A key aim is to identify and ensure the robustness of sources and collection methods in order to facilitate development of a Business Case that will provide solid and effectual argument of the value of the GerOnTe intervention.

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CONFIDENTIAL

APPENDIX 2: EORTC QLQ-C30

DUTCH

**EORTC QLQ-C30 (versie 3)**

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is? Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw initialen invullen:

--	--	--	--	--

Uw geboortedatum (Dag, Maand, Jaar):

--	--	--	--	--	--	--	--	--	--

De datum van vandaag (Dag, Maand, Jaar):

31

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	Helemaal niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2. Heeft u moeite met het maken van een <u>lange</u> wandeling?	1	2	3	4
3. Heeft u moeite met het maken van een <u>korte</u> wandeling buitenshuis?	1	2	3	4
4. Moet u overdag in bed of op een stoel blijven?	1	2	3	4
5. Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:

	Helemaal niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7. Was u beperkt bij het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8. Was u kortademig?	1	2	3	4
9. Heeft u pijn gehad?	1	2	3	4
10. Had u behoefte om te rusten?	1	2	3	4
11. Heeft u moeite met slapen gehad?	1	2	3	4
12. Heeft u zich slap gevoeld?	1	2	3	4
13. Heeft u gebrek aan eetlust gehad?	1	2	3	4
14. Heeft u zich misselijk gevoeld?	1	2	3	4
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (was u verstopt?)	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan.

DUTCH

Gedurende de afgelopen week:

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd bij uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het zich herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw <u>familieleven</u> in de weg staan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd bij uw <u>sociale</u> bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is?

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

APPENDIX 3: EORTC QLQ-ELD14

DUTCH

**EORTC QLQ-ELD14**

Soms zeggen patiënten dat ze volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze symptomen of problemen gedurende de afgelopen week heeft ervaren? Wilt u uw antwoord geven door het cijfer te omcirkelen dat het meest op u van toepassing is.

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
31. Heeft u moeilijkheden gehad met treden of trappen?	1	2	3	4
32. Heeft u problemen gehad met uw gewrichten (b.v. stijfheid, pijn)?	1	2	3	4
33. Voelde u zich onvast op uw benen staan?	1	2	3	4
34. Had u hulp nodig bij huishoudelijke klusjes zoals schoonmaken of boodschappen doen?	1	2	3	4
35. Heeft u zich in staat gevoeld om met uw familie over uw ziekte te praten?	1	2	3	4
36. Heeft u zich zorgen gemaakt over hoe uw familie met uw ziekte en behandeling omgaat?	1	2	3	4
37. Heeft u zich zorgen gemaakt over de toekomst van mensen die belangrijk zijn voor u?	1	2	3	4
38. Maakte u zich zorgen over uw gezondheid in de toekomst?	1	2	3	4
39. Voelde u zich onzeker over de toekomst?	1	2	3	4
40. Heeft u zich zorgen gemaakt over wat er zou kunnen gebeuren naar het einde van uw leven toe?	1	2	3	4
41. Heeft u in de afgelopen week een positieve kijk gehad op het leven?	1	2	3	4
42. Heeft u zich gemotiveerd gevoeld om uw normale hobby's en activiteiten voort te zetten?	1	2	3	4
43. In welke mate is uw ziekte een belasting voor u geweest?	1	2	3	4
44. In welke mate is uw behandeling een belasting voor u geweest?	1	2	3	4

APPENDIX 4: KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING (KATZ ADL)

Criterium	Score	Onafhankelijk (1 punt)	Afhankelijk (0 punten)
WASSEN	Wast zichzelf volledig onafhankelijk of wordt slechts geholpen voor één onderdeel (bv. het wassen van de rug of een gehandicapt lichaamsdeel)	Heeft hulp nodig bij het wassen van meer dan één lichaamsdeel; heeft hulp nodig om in en/of uit bad te komen of wacht zichzelf helemaal niet
KLEDEN	Neemt zelf de kledingstukken uit de kast of lade, kleedt zichzelf aan en kan losse kledingstukken zonder problemen aandoen. Het vastbinden van de schoenveters wordt niet beoordeeld	Heeft gedeeltelijke of volledige hulp nodig bij het kleden
WC-BEZOEK	Kan zich zonder hulp verplaatsen naar of van het toilet, zich neerzetten en rechtekomen van het toilet en zichzelf reinigen. Gebruik van mechanische hulpmiddelen is toegelaten	Heeft gedeeltelijke of volledige hulp nodig voor de verplaatsing naar het toilet, het reinigen of gebruikt een bedpan
VERPLAATSEN	Kan zich volledig zelfstandig in en uit een bed of een fauteuil verplaatsen. Gebruik van mechanische hulpmiddelen is toegelaten	Heeft hulp nodig om in en uit een bed of fauteuil te komen; doet geen zelfstandige verplaatsingen
CONTINENTIE	Is continent voor urine en faeces	Is volledig of gedeeltelijk incontinent voor urine of faeces
VOEDEN	Neemt het voedsel zelf van het bord en eet zelfstandig. Voorbereidende handelingen worden niet geëvalueerd	Heeft gedeeltelijke of volledige hulp nodig bij de voeding of heeft parenterale voeding nodig
Totaalscore (0-6)		

APPENDIX 5: CLINICAL FRAILTY SCALE

Score	Categorie fitheid	Toelichting
	1. Erg fit	Personen die krachtig, actief, energiek en gemotiveerd zijn. Deze ouderen doen regelmatig aan sport. Ze behoren tot de fitste voor hun leeftijd.
	2. Fit	Personen die geen actieve ziektesymptomen vertonen, maar minder fit zijn dan in categorie 1. Ze doen vaak aan sport of zijn occasioneel fysiek zeer actief, bijvoorbeeld seizoensgebonden.
	3. Gezond	Personen bij wie medische problemen goed onder controle zijn, maar die niet op regelmatige basis fysiek actief zijn op hun dagelijkse verplaatsingen na.
	4. Pre-frail	Personen die niet afhankelijk zijn van anderen voor dagelijkse activiteiten; maar bij wie symptomen vaak hun activiteiten beperken. Een vaak gehoorde klacht is langzamer zijn en/of vermoeidheid doorheen de dag.
	5. Mild frail	Deze personen zijn zichtbaar trager in hun activiteiten en hebben hulp nodig in de complexere iADL-taken (regelen van de financiën, transport, zware huishoudelijke taken, medicatie- beheer). (ADL onafhankelijk). De milde frailty zal geleidelijk aan volgende activiteiten belemmeren: alleen boodschappen doen en zich alleen buitenshuis verplaatsen, maaltijd bereiden en het uitvoeren van huishoudelijke taken.
	6. Matig frail	Deze personen hebben hulp nodig bij alle activiteiten buitenshuis en met huishoudelijke taken. Binnenshuis, hebben ze vaak problemen met trappen, en hebben ze hulp nodig bij het zich wassen, en hebben ze minimale begeleiding nodig bij het zich kleden (toezicht, aanwijzingen geven). (ADL gedeeltelijk afhankelijk).
	7. Ernstig frail	Volledig afhankelijk voor persoonlijke zorg ongeacht de oorzaak (fysiek of cognitief). Ondanks hun zorgnood lijken ze stabiel en lijkt er geen verhoogd risico op overlijden (binnen de 6 maanden). (ADL volledig afhankelijk).
	8. Zeer ernstig frail	Volledig afhankelijk en naderen het einde van het leven. Deze personen kunnen vaak niet herstellen van een mineure ziekte zoals een verkoudheid.
	9. Terminaal ziek	Deze categorie is van toepassing op personen die het einde van hun leven naderen met een levensverwachting ≤ 6 maanden, die anders niet duidelijk frail zijn.

APPENDIX 6: ECOG-PS

ECOG Performance Status	Graad
Normale activiteit zonder beperkingen.	0
Beperkt in activiteiten die een fysieke inspanning vereisen. In staat om te wandelen en licht werk uit te voeren.	1
Mobiel en volledig in staat tot zelfzorg. Niet in staat om enig werk te doen gedurende meer dan de helft van de dag.	2
In staat tot beperkte zelfzorg. Meer dan de helft van de dag gekluisterd aan bed of stoel.	3
Volledig invalide. Geen enkele mogelijkheid tot zelfzorg. Gekluisterd aan bed of stoel.	4
Dood	5
Score

APPENDIX 7: HADS

	Meestal	Vaak	Af en toe, soms	Helemaal niet
1. Ik voel me de laatste tijd gespannen.	3	2	1	0
2. Ik geniet nog steeds van de dingen waar ik vroeger van genoot.	3	2	1	0
3. Ik krijg de laatste tijd het angstige gevoel alsof er elk moment iets vreselijks zal gebeuren.	3	2	1	0
4. Ik kan lachen en de dingen van de vrolijke kant zien.	3	2	1	0
5. Ik maak me de laatste tijd ongerust.	3	2	1	0
6. Ik voel me de laatste tijd opgewekt.	3	2	1	0
7. Ik kan de laatste tijd rustig zitten en me ontspannen.	3	2	1	0
8. Ik voel me de laatste tijd alsof alles moeizamer gaat.	3	2	1	0
9. Ik krijg de laatste tijd een soort benauwd, gespannen gevoel in mijn maag.	3	2	1	0
10. Ik heb de laatste tijd geen interesse meer in mijn uiterlijk.	3	2	1	0
11. Ik voel me de laatste tijd rusteloos.	3	2	1	0
12. Ik verheug me van tevoren al op dingen.	3	2	1	0
13. Ik krijg de laatste tijd plotseling gevoelens van angst of paniek.	3	2	1	0
14. Ik kan van een goed boek genieten of een radio- of televisieprogramma.	3	2	1	0
Totaalscore HADS (0-42)			
Totaalscore oneven vragen HADS (0-21) – ANGST			
Totaalscore even vragen HADS (0-21) – DEPRESSIE			

APPENDIX 8: EQ-5D-5L

Vink onder elke titel het ENE vakje aan dat het best uw gezondheid VANDAAG beschrijft.

MOBILITEIT

- Ik heb geen problemen met rondwandelen ☐
- Ik heb een beetje problemen met rondwandelen ☐
- Ik heb matige problemen met rondwandelen ☐
- Ik heb ernstige problemen met rondwandelen ☐
- Ik ben niet in staat om rond te wandelen ☐

ZELFZORG

- Ik heb geen problemen met mijzelf te wassen of aan te kleden ☐
- Ik heb een beetje problemen met mijzelf te wassen of aan te kleden ☐
- Ik heb matige problemen met mijzelf te wassen of aan te kleden ☐
- Ik heb ernstige problemen met mijzelf te wassen of aan te kleden ☐
- Ik ben niet in staat mijzelf te wassen of aan te kleden ☐

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

- Ik heb geen problemen met mijn dagelijkse activiteiten ☐
- Ik heb een beetje problemen met mijn dagelijkse activiteiten ☐
- Ik heb matige problemen met mijn dagelijkse activiteiten ☐
- Ik heb ernstige problemen met mijn dagelijkse activiteiten ☐
- Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ☐

PIJN / ONGEMAK

- Ik heb geen pijn of ongemak ☐
- Ik heb een beetje pijn of ongemak ☐
- Ik heb matige pijn of ongemak ☐
- Ik heb ernstige pijn of ongemak ☐
- Ik heb extreme pijn of ongemak ☐

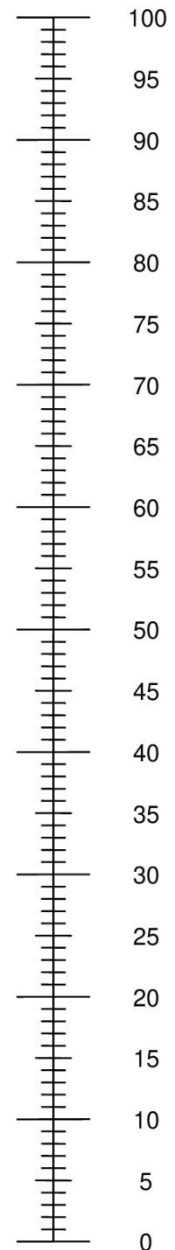
ANGST / DEPRESSIE

- Ik ben niet angstig of depressief ☐
- Ik ben een beetje angstig of depressief ☐
- Ik ben matig angstig of depressief ☐
- Ik ben erg angstig of depressief ☐
- Ik ben extreem angstig of depressief ☐

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal (te vergelijken met een thermometer) is genummerd van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen. 0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Plaats een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer nu het getal dat u aangeduid hebt op de meetschaal in het onderstaande vakje.

UW GEZONDHEID VANDAAG =

De beste gezondheid
die u zich kunt
voorstellen



De slechtste
gezondheid die u
zich kunt voorstellen

APPENDIX 9: ZARIT BURDEN INTERVIEW

	Bijna altijd	Redelijk vaak	Soms	Zelden	Nooit
1. Vindt u dat uw familielid meer hulp vraagt dan hij/zij nodig heeft?	4	3	2	1	0
2. Vindt u dat u niet genoeg tijd voor uzelf hebt omwille van de tijd die u doorbrengt met uw familielid?	4	3	2	1	0
3. Vindt u dat u onder druk staat door de combinatie van de zorg voor uw familielid en de andere verantwoordelijkheden die u probeert na te komen voor uw gezin of uw werk?	4	3	2	1	0
4. Schaamt u zich over het gedrag van uw familielid?	4	3	2	1	0
5. Bent u boos op uw familielid als u met hem/haar samen bent?	4	3	2	1	0
6. Vindt u dat uw familielid momenteel een negatieve invloed heeft op uw relatie met andere familieleden of vrienden?	4	3	2	1	0
7. Bent u bang voor wat de toekomst kan brengen voor uw familielid?	4	3	2	1	0
8. Vindt u dat uw familielid afhankelijk is van u?	4	3	2	1	0
9. Voelt u zich gespannen als u samen met uw familielid bent?	4	3	2	1	0
10. Vindt u dat uw gezondheid geleden heeft onder de zorg voor uw familielid?	4	3	2	1	0
11. Vindt u dat u omwille van uw familielid minder privacy hebt dan u zou willen?	4	3	2	1	0
12. Vindt u dat uw sociaal leven geleden heeft onder uw zorg voor uw familielid?	4	3	2	1	0
13. Voelt u zich ongemakkelijk bij het idee om vrienden te ontvangen omwille van uw familielid?	4	3	2	1	0
14. Vindt u dat uw familielid van u verwacht dat u voor hem/haar zorgt, alsof u de enige bent op wie hij/zij kan rekenen?	4	3	2	1	0
15. Vindt u dat u, naast uw andere uitgaven, niet genoeg geld hebt om voor uw familielid te zorgen?	4	3	2	1	0
16. Hebt u het gevoel dat u niet veel langer meer voor uw familielid zult kunnen zorgen?	4	3	2	1	0
17. Vindt u dat u de controle over uw eigen leven verloren hebt sinds uw familielid ziek werd?	4	3	2	1	0

18. Zou u eigenlijk de zorg over uw familielid het liefst willen overlaten aan iemand anders?	4	3	2	1	0
19. Voelt u zich onzeker over wat u met uw familielid moet doen?	4	3	2	1	0
20. Vindt u dat u meer zou moeten doen voor uw familielid?	4	3	2	1	0
21. Vindt u dat u beter voor uw familielid zou kunnen zorgen?	4	3	2	1	0
22. Hoe zwaar belast voelt u zich over het algemeen bij het zorgen voor uw familielid?	4	3	2	1	0
Totaalscore ZBI (0-88)				

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APPENDIX 10: P3CEQ

CONFIDENTIAL

START VAN HET INTERVIEW

Deze vragenlijst gaat over uw ervaringen met en uw inzicht in de zorg en ondersteuning die u heeft ontvangen van uw zorgverleners in de gemeente Medemblik gedurende de afgelopen [tijd].

De komende vragen gaan over 'zorg' die u ontvangen heeft. Met 'zorg' bedoelen wij alle zorg en ondersteuning die u heeft ontvangen op het gebied van uw gezondheid en welzijn.

Van wie heeft u gedurende de afgelopen [tijd] zorg ontvangen? Kruis aan wat van toepassing is, er zijn meerdere opties tegelijkertijd mogelijk.

Huisarts (incl. praktijkondersteuner)	<input type="checkbox"/>	(Wijk)verpleegkundige	<input type="checkbox"/>
Welzijnswerk	<input type="checkbox"/>	Geestelijke gezondheidszorg	<input type="checkbox"/>
Ziekenhuis (opname)	<input type="checkbox"/>	Ziekenhuis (poliklinisch)	<input type="checkbox"/>
Een therapeut (bijv. fysiotherapeut)	<input type="checkbox"/>	WMO ondersteuning vanuit de gemeente	<input type="checkbox"/>
Vrijwilligers (bijv. De Zonnebloem)	<input type="checkbox"/>	Anders, zoals	<input type="checkbox"/>

Indien u zorg heeft ontvangen van meerdere zorgprofessionals en/of informele hulpverleners, baseert u uw antwoord op de onderstaande vragen op uw algehele ervaring met deze zorg.

Gebruik a.u.b. bij iedere vraag de ruimte voor toelichting om relevante of opvallende voorbeelden te noteren.

- 1. Bespreekt u met uw zorgverlener(s) wat VOOR U het meest belangrijk is om te kunnen werken aan uw gezondheid en welzijn?**

Nooit	<input type="checkbox"/>	Toelichting
Soms	<input type="checkbox"/>	
Meestal	<input type="checkbox"/>	
Altijd	<input type="checkbox"/>	
Niet van toepassing	<input type="checkbox"/>	

2. Werd u voldoende betrokken bij beslissingen over uw zorg?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

3. Was er aandacht voor u als persoon en niet alleen voor uw ziekte of aandoening?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

4. Is het wel een voorgekomen dat u uw verhaal meerdere keren aan uw zorgverlener(s) moest vertellen?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

5. Vindt u dat de zorg die u van uw verschillende zorgverleners ontvangt goed op elkaar aansluit?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Er is maar één zorgverlener (bijv. de huisarts) van wie ik zorg ontvang		
Niet van toepassing		

6. Heeft u een aanspreekpunt vanuit de zorg(organisatie), die verantwoordelijk is voor het regelen van de zorg en ondersteuning die u ontvangt?

Ja		Toelichting:
Nee		
Weet ik niet		

7a. Heeft u een zorgplan waarin uw wensen op het gebied van uw gezondheid en welzijn zijn opgenomen?

Ja <i>Ga door naar de vragen 8b, 8c en 8d</i>		Toelichting:
Nee <i>Ga door naar vraag 9</i>		
Weet ik niet <i>Ga door naar vraag 9</i>		

7b. Heeft u een kopie van uw zorgplan thuis?

Ja		Toelichting:
Nee		
Weet ik niet		

7c. In hoeverre is het zorgplan bruikbaar VOOR U om aan uw gezondheid en welzijn te kunnen werken?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Weet ik niet		

7d. Denkt u dat alle zorgverleners, die betrokken zijn bij uw zorg, hetzelfde zorgplan gebruiken?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Weet ik niet		

8. Heeft u voldoende ondersteuning gekregen van uw zorgverlener(s) om aan uw gezondheid en welzijn te kunnen werken?

Ik heb geen ondersteuning nodig		Toelichting:
Ik heb geen ondersteuning gekregen		
Ik heb soms voldoende ondersteuning gekregen		
Ik heb vaak voldoende ondersteuning gekregen		
Ik heb altijd genoeg ondersteuning gekregen		
Niet van toepassing		

9. Kreeg u voldoende bruikbare informatie op het moment dat u dit nodig had, om te kunnen werken aan uw gezondheid en welzijn?

Ik ontvang geen informatie		Toelichting:
Ik ontvang soms voldoende informatie		
Ik ontvang vaak voldoende informatie		
Ik ontvang altijd voldoende informatie		
Ik ontvang te veel informatie		
Niet van toepassing		

10. Hoe zeker bent u ervan dat u in staat bent om zelf te werken aan uw gezondheid en welzijn?

Totaal niet zeker		Toelichting:
Niet zo zeker		
Redelijk zeker		
Erg zeker		
Niet van toepassing		

Optionele vraag, indien uw partner, kinderen of andere mantelzorgers bij uw afspraken met zorgverleners aanwezig zijn:

11. Werden uw partner, kinderen of andere mantelzorgers door uw zorgverlener(s) voldoende betrokken bij beslissingen over uw zorg?

Nooit		Toelichting:
Soms		

Meestal		
Altijd		
Ik wilde niet dat mijn partner, kinderen of andere mantelzorgers betrokken werden		
Mijn partner, kinderen of andere mantelzorgers wilden niet betrokken worden of waren hier niet toe in staat		
Ik heb geen partner, kinderen of andere mantelzorgers		

Hoe kan uw zorg worden verbeterd?

Welke zorg en ondersteuning kunnen u helpen om uzelf zekerder te voelen op het gebied van uw gezondheid en welzijn?

Overige opmerkingen:

Hartelijk dank voor het invullen van deze vragenlijst.

APPENDIX 11A: MAUQ (PATIENT INTERVENTION ARM VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app was makkelijk in gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	Het was makkelijk voor mij om de app te leren gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De navigatie was consistent bij het bewegen tussen schermen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	De interface van de app stelde me in staat alle functies te gebruiken (zoals informatie invoeren, op herinneringen reageren, informatie bekijken) die de app aanbiedt.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
5.	Telkens als ik een fout maakte met de app, kon ik die makkelijk en snel herstellen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
6.	Ik hou van de interface van de app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
7.	De informatie in de app was goed georganiseerd, zodat ik gemakkelijk de informatie kon vinden die ik nodig had.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
8.	De app gaf me voldoende bevestiging en informatie om me te laten weten hoe mijn actie vorderde.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
9.	Ik voel me op mijn gemak als ik deze app in een sociale omgeving gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
10.	De hoeveelheid tijd die in het gebruik van deze app gaat zitten, is passend voor mij.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
11.	Ik zou deze app opnieuw gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
12.	Over het algemeen ben ik tevreden met deze app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
13.	De app zou nuttig zijn voor mijn gezondheid	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

	en welzijn.		
14.	De app heeft mijn toegang tot de gezondheidszorg verbeterd.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
15.	De app heeft me geholpen mijn gezondheid effectief te beheren.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
16.	Deze app heeft alle functies en mogelijkheden die ik ervan verwachtte.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
17.	Ik kon de app zelfs gebruiken wanneer de internetverbinding slecht of niet beschikbaar was.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
18.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te ontvangen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS

APPENDIX 11B: MAUQ (PATIENT CONTROL ARM VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app zou nuttig zijn voor mijn gezondheid en welzijn.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	De app heeft mijn toegang tot de gezondheidszorg verbeterd.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De app heeft me geholpen mijn gezondheid effectief te beheren.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te ontvangen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

APPENDIX 12: MAUQ (PROVIDER VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app was makkelijk in gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	Het was makkelijk voor mij om de app te leren gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De navigatie was consistent bij het bewegen tussen schermen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	De interface van de app stelde me in staat alle functies te gebruiken (zoals informatie invoeren, op herinneringen reageren, informatie bekijken) die de app aanbiedt.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
5.	Telkens als ik een fout maakte met de app, kon ik die makkelijk en snel herstellen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
6.	Ik hou van de interface van de app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
7.	De informatie in de app was goed georganiseerd, zodat ik gemakkelijk de informatie kon vinden die ik nodig had.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

8.	De app gaf me voldoende bevestiging en informatie om me te laten weten hoe mijn actie vorderde.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
9.	Ik voel me op mijn gemak als ik deze app in een sociale omgeving gebruik.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
10.	De hoeveelheid tijd die in het gebruik van deze app gaat zitten, is passend voor mij.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
11.	Ik zou deze app opnieuw gebruiken.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
12.	Over het algemeen ben ik tevreden met deze app.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
13.	De app zou nuttig zijn voor mijn zorgpraktijk.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
14.	De app verbeterde mijn toegang tot het leveren van gezondheidsdiensten.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
15.	De app hielp me de gezondheid van mijn patiënten effectief te beheren.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
16.	Deze app heeft alle functies en mogelijkheden die ik ervan verwachtte.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
17.	Ik kon de app zelfs gebruiken wanneer de internetverbinding slecht of niet beschikbaar was.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
18.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te verlenen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS

CONFIDENTIAL

APPENDIX 13: AE/SAE FORM

Subject ID:				AE number:	
Date of awareness: ____/____/____ (only to be completed in case of SAE)				Follow-up number (as applicable):	
Description of event	Start date and time ____/____/____ ____:____ (if applicable)	Outcome <input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Not yet recovered <input type="checkbox"/> Death	Action taken regarding study intervention <input type="checkbox"/> None <input type="checkbox"/> Temporarily interrupted <input type="checkbox"/> Stopped permanently <input type="checkbox"/> Other:	Investigator	
				Seriousness	Severity
	Stop date and time ____/____/____ ____:____ (if applicable)		<input type="checkbox"/> None <input type="checkbox"/> Medication <input type="checkbox"/> Non-drug therapy <input type="checkbox"/> Further investigation performed <input type="checkbox"/> Other <input type="checkbox"/> Stop study due to AE	<input type="checkbox"/> NO <input type="checkbox"/> YES <i>If YES, tick all criteria that apply:</i> <input type="checkbox"/> Results in death ➔ Date of death: ____/____/____ <input type="checkbox"/> Is life-threatening <input type="checkbox"/> Results in permanent impairment <input type="checkbox"/> Requires or prolongs inpatient hospitalization ➔ Date of hospitalization: ____/____/____ ➔ Date of discharge: ____/____/____ <input type="checkbox"/> Medical or surgical intervention to prevent any of the outcomes above <input type="checkbox"/> Chronic disease <input type="checkbox"/> Led to fetal distress, fetal death, congenital abnormality or birth defect	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe

*Guidance for Sponsor: any SAE with a causal relationship to the IMD, comparator or procedure should be reported to the CA.

Report completed by:
 Date: ____/____/____ (dd/mm/yyyy)

Signature:

Report validated by Investigator:
 Date: ____/____/____ (dd/mm/yyyy)

Signature:

APPENDIX 14: DD FORM

Subject ID:		DD number: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up nbr:		
Event	Start date and time	Stop date and time	Origin of device deficiency	Action taken (Multiple actions possible, all applicable)

Describe event or deficiency:	Start: ____/____/____	Stop: ____/____/____	<input type="checkbox"/> Mechanical <input type="checkbox"/> Electronic <input type="checkbox"/> Software <input type="checkbox"/> Other: Type of device deficiency <input type="checkbox"/> Use error <input type="checkbox"/> Inadequate instructions <input type="checkbox"/> Device malfunction <input type="checkbox"/> Unknown <input type="checkbox"/> Not applicable <input type="checkbox"/> Other:	<input type="checkbox"/> None <input type="checkbox"/> Use of device temporarily interrupted <input type="checkbox"/> Visit termination <input type="checkbox"/> Resolved deficiency <input type="checkbox"/> Partially resolved <input type="checkbox"/> Other:
	Start time*: ____:____ (if applicable)	Stop time: ____:____ (if applicable)		
	<input type="checkbox"/> Unknown <i>*If onset time is unknown, enter time of first notice</i>	<input type="checkbox"/> Ongoing		

Report completed by:
 Date: ____/____/____ (dd/mm/yyyy)

Signature:

Report validated by Investigator:
 Date: ____/____/____ (dd/mm/yyyy)

Signature:

7.2. Annex 2: TWOBE protocol as submitted to Dutch authorities

STREAMLINED GERIATRIC AND ONCOLOGICAL EVALUATION BASED ON IC TECHNOLOGY FOR HOLISTIC PATIENT-ORIENTED HEALTHCARE MANAGEMENT FOR OLDER MULTIMORBID PATIENTS

TWOBE Protocol

Medical device investigation under the European Regulation 2017/745 on Medical Devices (MDR) Article 82

Version n°0.0 of 24/06/2022

This project has obtained funding from the Horizon 2020 Program - Topic H2020-SC1-BHC-24-2020

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KU LEUVEN/UZ LEUVEN

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APPROVAL AND SIGNATURES OF PROTOCOL

Title of protocol : Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients. TWOBE study.

Ethics Committee Belgium	Name: XXXXXXXX	Initial approval date	
		Reference	
Ethics Committee the Netherlands	Name: XXXXXXXX	Initial approval date	
		Reference	

Name and responsibility	Address	Date	Signature
Coordinating Investigator			

For Belgian sites: I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of December 22nd 2020 on medical devices, the Regulation (EU) 2017/745 of 5 April 2017 on medical devices, the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other applicable legal and regulatory requirements and Standard Operating Procedures (SOPs), and any subsequent amendments of the foregoing.

For Dutch sites: I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the Good Clinical Practice (decision of 24 November 2006), the Dutch law regarding medical research

involving human subjects (WMO), the EU General Data Protection Regulation 2016/679 (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (AVG).

I assume my responsibilities as referent investigator including:

- Collection of informed consent, dated and signed by participants before any selection procedure in the protocol,
- Validation of case report forms, completed for each participant included in the study,
- Direct access to source documents for verification by the clinical research assistant (CRA) commissioned by the sponsor,
- Archiving of critical documents of the study for a 25 year-period.

Name and address of the investigating centre:

Name of the Principal Investigator :

Date : |_|_| |_|_| |_|_|_|_|

Signature :

SYNOPSIS

Title of the study	Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients. TWOBE study.
Abbreviation of the trial	GerOnTe – TWOBE
Sponsor Identification	KU Leuven/UZ Leuven, Leuven, Belgium
Coordinating Investigator	Prof. Hans WILDIERS Department of General Medical Oncology, UZ Leuven, Belgium
National Principal Investigator for Belgium	Prof. Hans WILDIERS Department of General Medical Oncology, UZ Leuven, Belgium
National Principal Investigator for the Netherlands	Dr. Marije HAMAKER Department of Geriatrics, Diaconessenhuis, the Netherlands
Number of investigational sites planned	8 centres : - Belgium : 4 centres - The Netherlands : 4 centres
Number of participants	720 participants
Duration of the study	Planned enrollment period: 18 months Follow-up period: 12 months Study period: 36 months
Study rationale	<p>The heterogeneity of older patients in terms of health status, physical functioning and intrinsic capacity makes their evaluation complex. In those aged 65 to 84, the proportion of patients with multimorbidity is as high as 65% and rises to 81% in those aged 85 or older. Currently, in Europe, acute-hospital care is mainly single-disease oriented. As a result, coexisting morbidities are often under-evaluated and under-managed, leading to inappropriate drug prescriptions, avoidable hospital admissions, delays in treatment and ultimately to suboptimal care and unnecessary cost overruns. Moreover, because of different health organisations, management of older multimorbid patients varies from one country to the other while we know that the structure of health system organisation has a strong impact on patients' health status. Finally, none is currently structured to absorb the demographic increase of older patients.</p> <p>People with multimorbidity have reduced quality of life and impaired health outcomes and experience a significant impact of disease burden and an increased risk of death that current disease-centred management, which impacts patients' quality of life and quality of care, cannot manage.</p> <p>Disease-centred approach is not appropriate to manage these patients. Change to a patient-centred approach will simplify care pathways, secure management and treatment decision making and decrease healthcare costs. It will be a real breakthrough for daily practice with multiple impacts that must be quantified.</p> <p>The clinical model behind GerOnTe is to regroup all health professionals taking care of a multimorbid patient, into a common care coordination pathway: the Health Professional Consortium (HPC). The HPC will (i) centralise the decisions, aligning them to the patient's priorities, (ii) be assisted by an advanced practice nurse (APN) as case manager, and (iii) be facilitated by HolisTM GV data exchange, personalised</p>

	<p>for each patient. Patients will be stratified in order to determine their dominant disease, thus the appropriate HPC. Patient-centred health management by the HPC with availability of real time, hospital- and patient-based data will foster timely decision enabling avoidance of unnecessary procedures and treatments leading to reduction in number of ineffective treatments, complications and unscheduled hospitalisations, concerted treatments of multimorbidities, and to more patients staying at home thanks to self-management related reduction of dependence.</p> <p>The whole approach will be co-designed with patients, informal care givers and health professionals. Cancer is an excellent model to develop this approach in multimorbid patients because it is frequent and commonly associated with other morbidities in older patients but also because of its major impact on patients' general status and coexistent diseases. Cancer already benefits from a multidisciplinary management model that GerOnTe will enhance, strengthening exchange of holistic data, role of primary care and case management. GerOnTe will also provide new country-specific guidelines and best practices for implementation across Europe and for improved management of older multimorbid patients including improved quality of life and independent living at decreased costs.</p> <p>The GerOnTe project consists of two identical trials in two different European geographical areas, FRONE in France and TWOBE in Belgium and the Netherlands. The goal of two identical trials is to take into account the role of health care contexts in the implementation, effectiveness and efficiency of the GerOnTe intervention.</p>
Medical conditions	Multimorbid patient with new or progressive cancer (breast, lung, colorectal, prostate)
Objectives	<p>PRIMARY OBJECTIVE: to evaluate the effectiveness of the GerOnTe, ICT-based, integrated care pathway to improve patient 6-month quality of life, in Belgium and the Netherlands.</p> <p>SECONDARY OBJECTIVES</p> <ul style="list-style-type: none"> • Evaluate the effectiveness of the GerOnTe patient-centred system to: <ul style="list-style-type: none"> ○ Improve quality of life at 3, 9 and 12 months, ○ Improve patient survival and progression-free survival at 12 months, ○ Improve patient autonomy at 3, 6, 9 and 12 months, ○ Reduce patient anxiety at 3, 6, 9 and 12 months, ○ Reduce patient unscheduled hospitalisations and patient institutionalisations at 6 and 12 months, • Assess the cost-utility and cost-effectiveness of the GerOnTe intervention versus standard of care up to 1-year post-inclusion (3, 6, 9 and 12 months after inclusion), • Evaluate caregiver burden in health, psychological well-being, finances, social life and relationship with patient at 3, 6, 9 and 12 months, • Evaluate patient-reported overall experience of the GerOnTe intervention at 6 and 12 months, • Evaluate patient and health care professionals reported overall satisfaction and acceptability of the GerOnTe intervention at 6 and 12 months, • Analyze the implementation and use of the GerOnTe patient-centred intervention by patients and health care professionals
Study design	Study design is a stepped wedge randomized controlled trial. Clusters will be participating hospitals, comprising eight investigating sites in total. Patients

	<p>included at each “step” are different individuals. The first “step” is a reference measurement where none of the clusters will implement the intervention. The investigating sites will be randomly drawn to determine the order in which they will implement the intervention, by “steps” of two months.</p> <p>Each centre engaged to participate needs to participate till the end of the trial. A centre commitment to participate will be requested before each centre involvement to avoid centre withdrawal after the start of the trial.</p>
Inclusion criteria	<p><u>General inclusion criteria</u></p> <ol style="list-style-type: none"> 12. Age \geq 70 years old. 13. New or progressive cancer (breast, lung, colorectal, prostate) fulfilling the tumour specific criteria. 14. Estimated life expectancy greater than 6 months. 15. At least one moderate/severe multimorbidity inclusion criteria other than current cancer (see separate list under 5.3). 16. Patients must be willing and able to comply with study procedures. 17. Voluntarily signed and dated written informed consents prior to any study specific procedure. 18. QLQ-C30 Quality of Life Questionnaire fully completed at baseline, before inclusion. <p><u>Tumour specific inclusion criteria</u></p> <ol style="list-style-type: none"> 19. Specific inclusion criteria for breast cancer: <ol style="list-style-type: none"> 19.1. <u>Non-metastatic breast cancer (M0)</u>: <ul style="list-style-type: none"> • No prior treatment for the current breast cancer. • All 3 criteria required: <ul style="list-style-type: none"> ◦ Clinical staging: cT2-3-4 Nany, or cTany N1-2-3, ◦ The cancer specialist considers* surgery, ◦ The cancer specialist considers* radiotherapy and/or chemotherapy. 19.2. <u>Metastatic breast cancer (M1)</u>: Both criteria required: <ul style="list-style-type: none"> • The cancer specialist considers* chemotherapy or PARP-inhibitors or mTOR-inhibitors / PIK3CA inhibitors; Previous endocrine therapy +/- CDK4/6 inhibitors is allowed, • The patient received maximum 1 prior line of chemotherapy for metastatic disease. <p><i>*‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.</i></p> 20. Specific inclusion criteria for colorectal cancer: <ol style="list-style-type: none"> 20.1. <u>Non-metastatic colorectal cancer (M0)</u>: <ul style="list-style-type: none"> • No prior therapy for the current tumour in the recruiting hospital. • At least one of the 3 criteria required: <ul style="list-style-type: none"> ◦ The cancer specialist considers* surgery, ◦ The cancer specialist considers* radiotherapy, ◦ The cancer specialist considers* chemotherapy. 20.2. <u>Metastatic colorectal cancer (M1)</u>: <ul style="list-style-type: none"> • The cancer specialist considers* first line systemic therapy and/or radiotherapy (+/- surgery). No previous chemotherapy allowed except

adjuvant/perioperative chemotherapy stopped for more than 12 months.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

21. Specific inclusion criteria for **lung cancer**:

21.1. Non-metastatic lung cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery (patients considered for treatment with percutaneous thermoablation alone are not eligible),
 - The cancer specialist considers* radiotherapy (except SBRT),
 - The cancer specialist considers* systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

21.2. Metastatic lung cancer (M1):

- The cancer specialist considers* first or second line systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

22. Specific inclusion criteria for **prostate cancer**:

22.1. Non-metastatic prostate cancer (M0): one of the following:

- First diagnosis M0 prostate cancer (no therapy received yet for prostate cancer): at least one of the 2 criteria required:
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* hormone therapy (ADT +/- combination Abiraterone and Prednisone).
- Salvage treatment M0 prostate cancer (received prior surgery at least 6 months before):
 - The cancer specialist considers* radiotherapy (+/- ADT)
- Non-metastatic castration resistant prostate cancer:
 - The cancer specialist considers* treatment intensification (ADT + Enzalutamide or Apalutamide or Darolutamide).

22.2. Metastatic prostate cancer (M1):

- The cancer specialist considers* treatment with Abiraterone or Enzalutamide or Apalutamide or Docetaxel or Cabazitaxel or PARP-inhibitors or Lutetium PSMA.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

Exclusion criteria	<p>5. Mental illness/cognitive impairment that limits ability to provide consent or complete trial procedures.</p> <p>6. Participating to an interventional clinical trial with a non-registered anticancer drug or to another geriatric intervention trial.</p> <p>7. Patients and caregivers are unable or unwilling to use ICT-devices (tablet, computer, smartphone) or the Internet according to protocol.</p> <p>8. Patient already included in this study.</p>
Control arm	Patients included in the control arm will be managed according to the standard of care.
Intervention schedule	<p>The intervention will include the following components:</p> <ul style="list-style-type: none"> • A health professional consortium (HPC) for each patient, which will work together to make recommendations regarding oncologic treatment and non-oncologic interventions, at baseline and in the course of treatment. This will be in addition to the usual multidisciplinary tumour board (MTB) which will provide oncologic treatment recommendations based on the usual oncologic work-up. • An advance practice nurse (APN) as case-manager, who will be the primary contact person for the patient during the oncologic treatment and subsequent follow-up • A baseline patient evaluation consisting of a comprehensive geriatric assessment by a geriatrician or APN, which will focus on general health status, comorbidities and intrinsic capacity. Baseline documentation of patient preferences and priorities will be done by the APN. • A health care professional dashboard called Holis Dashboard, which 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 the standard consensus dataset. Dashboard data will be made available selectively to all health care professionals of the HPC. • A patient application called Holis Patient Application, which will allow for monitoring of symptoms and signs of destabilised comorbidity or functional decline during and after treatment, with additional self-management library with recommendations for how the patient can deal with issues or for contacting their health care providers in case of symptoms requiring urgent intervention. • Additional data that will be collected every 3 months are quality of life questionnaires (EORTC QLQ-C30/QLQ-ELD14/EQ-5D-5L), autonomy questionnaire (Katz ADL), anxiety/depression questionnaire (HADS), patient-related outcomes questionnaire (perceived benefit, treatment objectives, tool satisfaction) and possible revision of patient's treatment objectives.
Endpoints	<p>PRIMARY ENDPOINT</p> <p>Quality of life assessed by the EORTC QLQ-C30 questionnaire at 6 months after GerOnTe inclusion using 3 derived scores of the QLQ-C30 questionnaire:</p> <ul style="list-style-type: none"> • Normalized global health status score • Normalized score of the physical functioning scale • Normalized score of the emotional functioning scale <p>SECONDARY ENDPOINTS</p> <p>11. Quality of life</p> <ul style="list-style-type: none"> • The 3 normalized QLQ-C30 scores at baseline 3, 9 and 12 months

	<ul style="list-style-type: none"> • Normalized scores of QLQ-C30 scales/items (role functioning scale, cognitive functioning scale, social functioning scale, fatigue scale, nausea scale, pain scale, dyspnea item, insomnia item, appetite loss item, constipation item, diarrhea item and financial difficulties item) at baseline, 3, 6, 9 and 12 months. • Scores of QLQ-ELD14 scales/items (mobility scale, worries about others scale, future worries scale, maintaining purpose scale, burden of illness scale, joint stiffness item, family support item) at baseline, 3, 6, 9 and 12 months <p>12. Survival: Overall survival at 12 months and progression-free survival (the time from study treatment initiation to the first occurrence of disease progression or death, whichever occurs first).</p> <p>13. Patient autonomy, frailty and weight evolution</p> <ul style="list-style-type: none"> • Dependence score of the Activities of Daily Living scale (Katz ADL) at baseline, 3, 6, 9 and 12 months, • Proportion of patients living at home at 6 and 12 months, • Number of completed chair stands in 30 seconds (Chair stand test) at baseline, 3, 6, 9 and 12 months, • Score of the Clinical Frailty Scale at baseline, 3, 6, 9 and 12 months, • Grade of performance status, measured by ECOG-PS at baseline, 3, 6, 9 and 12 months, • Weight at baseline, 3, 6, 9 and 12 months. <p>14. Patient anxiety: Score of Hospital Anxiety and Depression Scale (HADS) at baseline, 3, 6, 9 and 12 months.</p> <p>15. Proportion of patient institutionalized and number of unscheduled hospitalisations per participants at 6 and 12 months.</p> <p>16. Cost per life years gained (CEA, derived from survival/progression-free survival), cost per QALY gained (CUA, using utility assessed through normalized scores of EQ-5D-5L questionnaire collected at baseline, at 3, 6, 9 and 12 months after inclusion) and incremental cost-effectiveness ratios (ICERs) obtained by a cost-utility and a cost-effectiveness analysis.</p> <p>17. Caregiver burden in health, psychological well-being, finances, social life and relationship with patient, using the Zarit Burden Interview at baseline, 3, 6, 9 and 12 months</p> <p>18. Patient reported overall experience of person-centred coordinated care measured through the Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) at 6 and 12 months.</p> <p>19. Patient, physician and health-care-professionals-reported overall satisfaction with the ICT of the GerOnTe system: Score derived from the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps using the patient version for patient satisfaction and the provider version for physician and health care professional at 6 and 12 months after inclusion.</p> <p>20. GerOnTe patient-centred system implementation and usage evaluated at 6 months (use of the Holis Patient App measures, for instance: number and frequency of connections to the app by patients; number of web-based meetings with APN by site)</p>
Statistical considerations	<p><u>Hypothesis and number of participants needed</u></p> <p>Sample size calculation was drawn to detect a mean difference of 10 points or more (on a score from 0 to 100) (Osoba 1998), should the intervention be effective, for at least one of the three targeted health-related quality of life (HRQoL) scores (common standard deviation of 20 points). If the GerOnTe intervention improves at least one of the three scores by at least 10 points, the intervention is considered</p>

effective. If the GerOnTe intervention improves one of the 3 subscores by 10 or more points and decrease another subscore by 10 or more points, the intervention will be considered effective. In that unlikely situation, the GerOnTe scientific committee will conduct and communicate a clinical analysis and clinical interpretation.

With a 1.6% two-sided type I error (accounting for the 3 comparisons), a statistical power of 90%, and accounting for a possible 20% dropouts, the total minimum number of patients to be included is 278. 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 corresponding to 10 patients on average per step and per centre.

Definition of study population

Main analysis will be performed among the intention-to-treat population: all patients will be included in the analysis in the group in which they were initially randomised and all their data will be used.

A per protocol population can be used in secondary analysis including only patients who are strictly compliant with the procedure (lost-of-follow-up will be, in particular, excluded).

Statistical analysis

Descriptive analysis will always be presented overall and by treatment group.

The primary endpoint is the Quality of Life assessed by the EORTC QLQ-C30 (version 3.0) questionnaire at 6 months after GerOnTe implementation. It has 3 sub-scores that will be analyzed independently, with alpha risk adjustment.

In order to take into account, the stepped wedge study design and its specificities (possible temporal effect, variable cluster size, presence of clusters), generalized mixed linear models will be used (Husset & Hughes 2007). Since the variables to be explained are quantitative (normalized scores), mixed linear regression models will be used. Random effects on the site, the time and the time of measurement (before/after the intervention is implemented) will be introduced where possible. The multiplicity of tests will be taken into account by adjusting the p-value using a Family-wise error rate method (Burman Stat Med 2009).

Secondary endpoints will be analyzed using the same strategy as the primary endpoints. Longitudinal data (repeated measure across the 4 follow-up times) can be analyzed adding a random effect on the patient.

Concerning the cost-utility and cost-effectiveness analysis:

The economic evaluation will be conducted from a societal perspective for primary analysis (which accounts both the costs in the public payer perspective and other direct and indirect costs relevant for different stakeholders, including patients). A secondary analysis will additionally be conducted from the payer perspective only, with the aim to estimate the budgetary impact on public finances. In this case, only the resource used within the hospital setting will be considered.

Costs will be calculated considering resource use at patient level and unit costs of each product/service used in the care pathway. 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 available sources. A map of available patient-level RWD (Real World Data) will be created to generate real-world evidence. Time spent will be

	measured by microcosting (through interviews and questionnaires) and will inform the economic analysis.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of Daily Living scale
ADT	Androgen Deprivation Therapy
APN	Advanced Practice Nurse
ARS	Regional Health Agency
CEA	Cost per life years gained
CGA	Comprehensive Geriatric Assessment
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Assistant
CRF	Case Report Form
CUA	Cost per QALY gained
CVA	Cerebrovascular Accident
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
DQF	Data Query Forms
EC	Ethics Committee
ECOG	Eastern Collaborative Oncology Group
EHR	Electronic Health Report
EMR	Electronic Medical Record
EORTC	European Organisation for Research and Treatment of Cancer
FAMHP	Federal agency for Medicines and Health Products
FG	Focus Groups
FNCLCC	Federation of Anti-Cancer Centres
GCP	Good Clinical Practice
GDPR	General Data Protection regulation
GP	General Practitioner
GV	Geriatric Version
HADS	Hospital Anxiety and Depression Scale
HPC	Health Professionals Consortium
HRQoL	Health Related Quality of Life

ICER	Incremental Cost-Effectiveness Ratio
ICT	Information Communication Technology
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention To Treat
LYG	Life Years Gained
MAUQ	mHealth App Usability Questionnaire
MDT	Multi-disciplinary Team
MTB	Multidisciplinary Tumour Board
NOAC	Novel Oral Anticoagulant
P3CEQ	Person-Centred Coordinated Care Experience Questionnaire
PFS	Progression-Free Survival
PROMs	Patient-Reported Outcome Measures
PS	Performance Status
QALY	Quality Adjusted Life Year
QKPI	Quality Key Performance Indicators
QLQ-C30	Quality of Life Questionnaire – Core 30 items
QLQ-ELD14	Quality of Life Questionnaire – Elderly Cancer Patients 14 items
RWD	Real World Data
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SNDS	National Health Data System
SOP	Standard Operating Procedure
TCO	Total Cost of Ownership
TDABC	Time-Driven Activity-Based Costing
TSC	Trial Steering Committee
ZBI	Zarit Burden Interview

20. CONCEPT AND RATIONALE OF THE TRIAL

20.1. MANAGEMENT OF MULTIMORBID PATIENTS

The heterogeneity of older patients in terms of health status, physical functioning and intrinsic capacity makes their evaluation complex. In those aged 65 to 84 years, the proportion of patients with multimorbidity is as high as 65% and rises to 81% in those aged 85 or older (Barnett Lancet 2012). The most prevalent morbidities in patients older than 65 are arthritis (57%), hypertension (55%), pulmonary disease (38%), diabetes (17%), cancer (17%), and osteoporosis (16%) (Vogelli J Gen Int Med 2007). Cardiovascular diseases are among the most frequent and the most lethal morbidities in older patients, followed by chronic obstructive pulmonary disease, diabetes, and cancer (Menotti J Clin Epidemiol 2001). Currently, in Europe, acute-hospital care is mainly single-disease oriented (with the exception of geriatricians who perform holistic evaluation and management of patients) (Rijken Health Policy 2018). As a result, coexisting morbidities are often under-evaluated and under-managed, leading to inappropriate drug prescriptions, avoidable hospital admissions (Leendertse Arch Int Med 2008), delays in treatment and ultimately to suboptimal care and unnecessary cost overruns (Ernst J Am Pharm Assoc 2001). Moreover, because of different health organisations, management of older multimorbid patients varies from one country to the other (Kringos Br J Gen Pract 2013) while we know that the structure of health system organisation has a strong impact on patients' health status (Hansen Health Affairs 2015). Finally, current health systems are not structured to absorb the demographic increase of older patients.

People with multimorbidity have reduced quality of life and impaired health outcomes (Salisbury Lancet 2012) and experience a significant impact of disease burden (Rose Qual Life Res 2018; Bayliss Health Qual Life Outcomes 2005) and an increased risk of death (Pereira-Nunez Arch Gerontol Geriatr 2016) that current disease-centred management, which impacts patients' quality of life and quality of care, cannot manage. Without appropriate coordination of care, despite attention and good will of health professionals, because of their intrinsic medical complexity, multimorbid patients may experience multiple problems including interaction between medications or adverse consequences of expected and unexpected events on other morbidities, among other causes. These events will often lead to unscheduled events or hospitalisations, thus impairing quality of life, and even to death in some cases. This is why there is an imperative to develop solutions to effectively manage this complexity.

The current situation should be addressed at a European level and needs benchmarking practices as well as the development of shared, automated and cost-effective solutions for better global implementation. GerOnTe builds on the findings of past EU projects (PHAMEU, SIMPHS, ICARE4EU, JA-CHRODIS and SELFIE) to develop appropriate solutions for the management of patients and to facilitate availability of data to health professionals as well as patients and their informal caregivers, in order to improve care of multimorbid and vulnerable patients (Berntsen J Med Internet Res 2019).

The effective management of patients with multiple morbidities is a key task for healthcare systems, and accounts for a significant part of total healthcare expenditure (Picco BMC Health Serv Res 2016; König BMC Health Serv Res 2013) with wide variability in terms of complexity. Indeed, each multimorbid patient combines different morbidities and medications with a specific medico-social background, leading to multiple possibilities of interactions, which should be understood to prevent unexpected consequences.

The best solution to consider this context is to move towards patient-centred management. Achieving this effectively, and affordably, will require an organisation shift from disease-centred care delivery to patient-centred integrated care delivery. Organisation of care, simultaneous availability of health professionals and resistance to change in organization and work habits will be key issues for which we will need to develop strong arguments based on facts i.e. data from clinical trials with a large set of endpoints directed towards end users and health authorities. It is therefore of crucial importance to develop models based on Total Cost of Ownership (TCO), which will enable organisations to understand cost impacts over time. To avoid

unnecessary interventions, the treatment decision-making process should involve all types of health professionals concerned, and present to all of them concomitantly exhaustive and personalised relevant data for each patient. Above all, the patient's own perception and opinion, and that of their informal caregivers, need to be taken into account during the whole care process. To this end, it is necessary to develop specific social and economic Quality Key Performance Indicators (QKPIs), in order to evaluate the quality of care for people with multimorbidity.

The choice to start in the context of care of multimorbid patients having cancer as a dominant morbidity is motivated by the fact that:

- cancer frequency increases sharply with age for most cancer types and is thus common in older adults, affect 45 to 55% of patients older than 70 (<https://www.cancerresearchuk.org/health-professional/cancerstatistics/incidence/age#heading-Zero>; Defossez Francim 2019);
- cancer and its aggressive treatments have a strong impact on patients' general status, on other co-occurring diseases, and on their treatments;
- at EU-level, a multidisciplinary approach is standard practice for cancer management, minimising the step-change required for real-life validation of GerOnTe during the lifetime of the project;
- once validated, this model will be applicable to any other combination of morbidities with or without cancer, giving to the concept a major potential of generalisability for the older population.

20.2. THE GERONTE CARE SYSTEM

For care in cancer patients, recent data show that real-time information about events during follow-up is useful and that web-based prospective weekly collection of symptoms improves survival (Denis J Natl Cancer Inst 2017, Basch JAMA 2017) and quality of life (Basch J Clin Oncol 2016). Cancer is frequently associated with other morbidities, particularly depression and anxiety, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, and pain, especially in socioeconomic deprived populations (Barnett The Lancet 2012). Multimorbidity is a major cause of reduced survival in all cancer types. Long-term vulnerability and loss of intrinsic capacity are common in older patients, particularly when they develop cancer, which increases risks through the disease itself and its treatment. Cancer is thus an excellent model to validate optimisation of multimorbid patient management pathways because of (i) its strong impact on the patient's general well-being and on other coexistent diseases, and (ii) the potential consequences of its aggressive treatments on other morbidities and their management. GerOnTe will build upon existing multidisciplinary in cancer management (cancer specialists including surgeons, radiation and medical oncologists, as well as geriatricians, radiologists, pathologists, general practitioners, organ specialists, supportive care specialists, nurses, physiotherapists, dieticians, and occupational therapists), bringing a novel use of case management and a strengthened role of primary care thanks to GerOnTe care pathway.

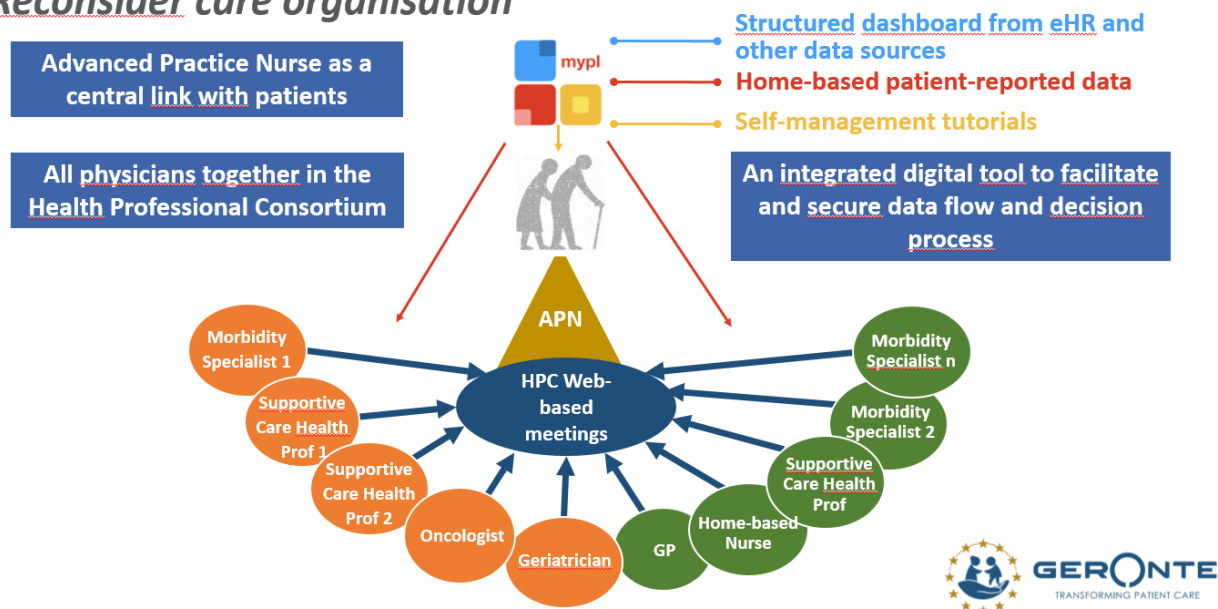
For optimal treatment decisions in the complex scenario of multimorbid patients, numerous existing medical, lifestyle and patient-reported data must be made available to health professionals at the time of treatment decision and patient follow-up. Although progress is hampered by the routine exclusion of multimorbid patients from clinical trials (Jadad JAMA 2011), it is widely accepted by clinicians that data required for treatment decisions include detailed evaluation of the patient's overall health status (including clinical background with multimorbidity, intrinsic capacity and patient preferences) which can be routinely performed by trained geriatricians using Comprehensive Geriatric Assessment (CGA). CGA is recognized as best practices for older cancer patients and is available through learned societies such as SIOG (Societe Internationale d'Oncologie Geriatrique), a Partner in the GerOnTe consortium. CGA is performed in patients with probable frailty according to a screening questionnaire such as G8 (Soubeyran Plos One 2014). The prognostic value of CGA in cancer patients has been demonstrated: CGA identifies patients at risk of early death (Soubeyran J Clin Oncol 2012), early functional decline (Hoppe J Clin Oncol 2013) and severe toxicities (van Walree J Ger Oncol 2019). Currently, too few patients benefit from CGA because it is

considered too time-consuming despite the fact that this assessment increases efficiency and cost-effectiveness by enabling avoidance of unnecessary procedures and treatments as well as complications (Hamaker J Clin Oncol 2017).

The clinical model behind GerOnTe is to regroup all health professionals taking care of a multimorbid patient, into a common care coordination pathway, the Health Professional Consortium (HPC). The HPC will (i) centralise the decisions, aligning them to the patient's priorities, (ii) be assisted by an Advanced Practice Nurse (APN) as case manager, and (iii) be facilitated by HolisTM GV data exchange, personalised for each patient. Patients will be stratified in order to determine their dominant disease, thus the appropriate HPC. Patient-centred health management by the HPC, with availability of real time, hospital- and patient-based data, will foster timely decisions enabling avoidance of unnecessary procedures and treatments leading to a reduction in the number of ineffective treatments, complications and unscheduled hospitalisations, concerted treatments of multimorbidities and to more patients staying at home thanks to self-management related reduction of dependence.

GERONTE patient-centred management

Reconsider care organisation



21. OBJECTIVES

21.1. PRIMARY OBJECTIVE

The primary objective of GerOnTe TWOBE is to evaluate the effectiveness of the GerOnTe, ICT-based, integrated care pathway to improve patient 6-month quality of life, in Belgium and the Netherlands.

21.2. SECONDARY OBJECTIVES

The secondary objectives of GerOnTe TWOBE are, in the context of a Belgian and Dutch health-system organisation, to:

- Evaluate the effectiveness of the GerOnTe patient-centred system to:
 - Improve quality of life at 3, 9 and 12 months (secondary endpoint #1),
 - Improve patient survival and progression-free survival at 12 months (secondary endpoint #2),
 - Improve patient autonomy and minimize frailty and weight evolution at 3, 6, 9 and 12 months (secondary endpoint #3),
 - Reduce patient anxiety at 3, 6, 9 and 12 months (secondary endpoint #4),
 - Reduce patient unscheduled hospitalisations and patient institutionalisations at 6 and 12 months (secondary endpoint #5);
- Assess the cost-utility (through a cost-utility analysis – CUA) and the cost-effectiveness (through a Cost-Effectiveness Analysis – CEA) of the GerOnTe intervention versus standard of care up to 1-year post-inclusion (3, 6, 9 and 12 months after inclusion) (secondary endpoint #6);
- Evaluate caregiver burden in health, psychological well-being, finances, social life and relationship with patient at 3, 6, 9 and 12 months (secondary endpoint #7);
- Evaluate patient-reported overall experience of the GerOnTe intervention at 6 and 12 months post-inclusion (secondary endpoint #8);
- Evaluate patient and health care professionals reported overall satisfaction and acceptability of the GerOnTe intervention at 6 and 12 months (secondary endpoint #9);
- Analyze the implementation and use of the GerOnTe patient-centred intervention by patients and professionals (secondary endpoint #10).

21.3. ANCILLARY STUDY OBJECTIVE

The general objective of the ancillary study, as detailed in the appendix 1, is to support the economic, implementation evaluation, and the development of a business case of the GerOnTe model.

The specific objectives of this study are to:

3. Identify, describe, analyse, and map the common and distinctive elements of the current care pathways for older multimorbid patients (with cancer as a primary condition) in Belgium and the Netherlands within each clinical sites involved before the implementation of GerOnTe,
4. Describe and analyze the process of implementation of the intervention in the trial sites beyond the specific trial outcomes to enable analysis of the mechanism of action of the intervention, the contextual factors and barriers and facilitators to implementation (to develop a comprehensive implementation guide that will inform implementation across diverse settings).

In each clinical site, the ancillary study will involve approximately 3-5 staff members (e.g., principal investigator, clinicians, nurses, administrators) and 5-10 patients and/or family members/caregivers over the entire duration of the project.

22. STUDY ENDPOINTS

22.1. PRIMARY ENDPOINT

Quality of life assessed by the EORTC QLQ-C30 (version 3.0, appendix 2) questionnaire at 6 months after inclusion.

Three derived scores of the QLQ-C30 questionnaire are considered as primary endpoints:

- Normalized global health status score of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100),
- Normalized score of the physical functioning scale of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100),
- Normalized score of the emotional functioning scale of the QLQ-C30 (version 3.0) questionnaire at 6 months after inclusion (score 0-100).

22.2. SECONDARY ENDPOINTS

12. Quality of life

- Normalized 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 after inclusion.
- Normalized scores of the following QLQ-C30 scales/items assessed at baseline, 3, 6, 9 and 12 months after inclusion: role functioning scale, cognitive functioning scale, social functioning scale, fatigue scale, nausea scale, pain scale, dyspnea item, insomnia item, appetite loss item, constipation item, diarrhea item and financial difficulties item.
- Scores of the following QLQ-ELD14 scales/items (appendix 3) assessed at baseline, 3, 6, 9 and 12 months after inclusion: assess mobility scale, worries about others scale, future worries scale, maintaining purpose scale, burden of illness scale, joint stiffness item, family support item. The QLQ-ELD14 questionnaire is a complementary module to the QLQ-C30 and taking into account the specific needs of older patients.

13. Survival

- Overall survival at 12 months after inclusion,
- Progression-free survival (PFS) defined as the time from study treatment initiation to the first occurrence of disease progression or death (of any cause), whichever occurs first.

14. Patient autonomy, frailty and weight evolution

- Dependence score of the Activities of Daily Living scale (Katz ADL) (appendix 4) assessed at baseline, 3, 6, 9 and 12 months after inclusion,
- Proportion of patients living at home at 6 and 12 months after inclusion,
- Number of completed chair stands in 30 seconds (Chair stand test: participants stand up repeatedly from a chair for 30 seconds) at baseline, 3, 6, 9 and 12 months after inclusion.,
- Score of the Clinical Frailty Scale (appendix 5) at baseline, 3, 6, 9 and 12 months after inclusion,
- Grade of performance status, measured by ECOG-PS (appendix 6) at baseline, 3, 6, 9 and 12 months after inclusion,
- Weight at baseline, 3, 6, 9 and 12 months after inclusion.

15. Patient anxiety

Score of HADS (appendix 7) at baseline, 3, 6, 9 and 12 months after inclusion.

16. Patient institutionalisation and unscheduled hospitalisations

- Proportion of patients institutionalised (see definition in section 7.1.3) at baseline, 6 and 12 months after inclusion.
- Proportion of patients with at least one unscheduled hospitalisation and number of unscheduled hospitalisations per patient (see definition in section 7.1.4) during 12 months after inclusion.

17. Cost-utility and cost-effectiveness analysis

- Cost per life years gained (CEA), cost per QALY gained (CUA) and incremental cost-effectiveness ratios (ICERs) obtained by a cost-utility and a cost-effectiveness analysis. Life years gained (LYG) in the CEA will be derived from a clinical metric (overall survival/progression-free survival) that will be measured at 6 and 12 months,
- Quality-adjusted life years (QALYs) in the cost per QALY gained (CUA) calculated using utility assessed through normalised scores of EQ-5D-5L questionnaire (appendix 8) collected at baseline, 3, 6, 9 and 12 months after inclusion. It includes the 5-level questions covering five dimensions.
- Resource use data during the 12 months of patient follow-up will include all direct and indirect costs and will be collected through:
 - Trial case report forms (CRFs) completed by the study collaborator or the APN,
 - Electronic medical records (EMRs) and electronic patient files linked to the patient sample by deterministic matching,
 - Patient questionnaires (e.g., patient report the frequency of visits to the medical specialist, APN, general practitioner). Questionnaires will be completed at baseline and at 3, 6, 9 and 12 months.
- Caregiver: questionnaire for the measurement, valuation and estimation of costs of informal care.
- Results will be presented as:
 - cost per life years gained (CEA),
 - cost per QALY gained (CUA),
 - Incremental cost-effectiveness ratios (ICERs).

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

Total burden will be obtained using the Zarit Burden Interview (Zarit et al, 1980; Hagell et al 2017) (appendix 9) by adding the scores across all 22 items, assessed at baseline, 3, 6, 9 and 12 months after inclusion.

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

Patient experience measured through the Person-Centred Coordinated Care Experience Questionnaire (P3CEQ) - 11 items (Lloyd et al 2019) (appendix 10) and a question about worth of treatment, both at 6 and 12 months after inclusion.

20. Patient, physician and health-care-professionals-reported overall satisfaction with the ICT of the GerOnTe intervention

Patient satisfaction and usability of mHealth application within the GerOnTe intervention will be evaluated by using the score derived from the 21-items mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (Zhou et al 2019) (appendix 11A and 11B) at 6 and 12 months after inclusion.

Physician and health-professional satisfaction and usability of mHealth application within the GerOnTe intervention will be evaluated by using the score derived from the adjusted version designed for health care providers of the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Provider version) (Zhou et al 2019) (appendix 12), consisted of 18 items, at 6 and 12 months after inclusion.

21. GerOnTe patient-centred system implementation and usage

GerOnTe patient-centred system implementation and usage will be evaluated at 6 months and 12 months after inclusion:

- Number and frequency of connections to the Holis Patient App,
- Duration of logins and activities with the Holis Patient App,
- 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 PROM's dashboards completed by patient,
- Number of health professional meetings (Multidisciplinary Tumour Boards (MTB) or other morbidities treatment decision) involving complete dashboards analysis by site.

Because no adverse event is expected to be generated by the GerOnTe intervention, the research protocol does not plan any assessment of traditional safety endpoints. However, the implementation and usage of the GerOnTe intervention, which are particularly important issues in understanding its effectiveness, will be carefully evaluated. As such, if any event that could be characterised as adverse event or serious adverse event (as defined in the section 12. MANAGEMENT OF ADVERSE EVENTS / SIDE EFFECTS / INCIDENTS) occurred, those events would be fully reported and described.

22. Ancillary study

Ancillary study is fully described in appendix 1.

23. STUDY DESIGN

23.1. TYPE OF TRIAL

Study design is a stepped wedge randomised controlled trial. Clusters will be participating hospitals, comprising eight investigating sites in total (Figure 2).

This is a stepped wedge of cross-over type. Patients included at each "step" are different individuals. The first "step" is a reference measurement where none of the clusters will implement the intervention. The investigating sites will be randomly drawn to determine the order in which they will implement the intervention, by "steps" of two months. A total of 10 patients by step are to be included in each centre; these 10 patients must be regularly included along the 2-month period of each step. If 10 patients are

already included before the end of the 2 months' step period, the centre has to stop the inclusions till the beginning of the subsequent step. If a centre, near to the end of a step, is far from reaching of the 10 patients' inclusion, it must increase the speed of its inclusions to be as close as possible of 10 patients included at the end of the step. In each centre, patient sample has to be representative of type of cancer managed in the centre, along the trial duration. The repartition of cancer types must be homogeneous along the steps and during the trial duration.

All participating investigating sites will have study collaborators in charge of organizing intervention implementation and data collection. The intervention will be prepared prior to the start of the trial, so that each investigating site can implement it as defined by the randomisation. Each centre engaged to participate needs to participate till the end of the trial. A centre commitment to participate will be requested before each centre involvement to avoid centre withdrawal after the start of the trial. Quantitative data regarding the Holis Patient App usage will be collected at each step and in each cluster by study collaborators, from the beginning of GerOnTe intervention implementation. Care outcome data (Quality of life, anxiety, autonomy, additional hospitalisation, mortality...) will be collected by local referents at baseline and at 3, 6, 9 and 12 months after inclusion in GerOnTe. The data necessary to calculate the real cost of the intervention, of its implementation and of resource use data of patient management will be continuously collected during follow-up. GerOnTe patient-centred intervention implementation and usage will be collected by the local referents in each centre. Qualitative analysis will be performed in each centre at GerOnTe intervention implementation and during follow-up.

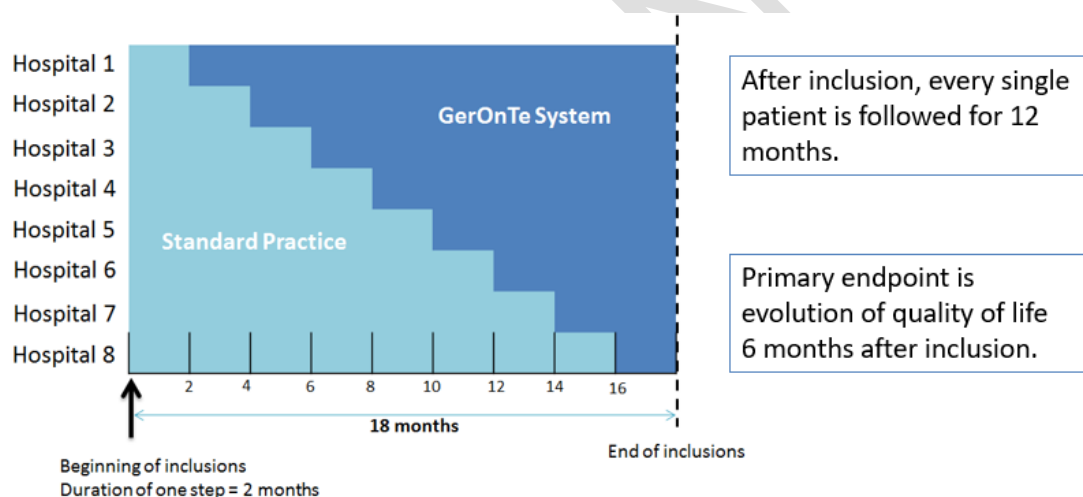


Figure 2: Schematic representation of GerOnTe TWOBE stepped wedge cross-designed for inclusion of 720 patients across eight sites.

The randomisation list will be established by the statistician at the Methodology and Data Management Centre of Institut Bergonié prior to the start of the research using SAS software. A document describing the randomisation procedure will be kept confidential within the Methodology and Data Management Centre of Institut Bergonié.

In this stepped wedge trial, the order of integration of the intervention in the sites will be randomised. The intervention will be implemented in a single site at each "step" to ensure optimal power. The centres will be informed at the outset when the intervention will be implemented.

23.2. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 30 months, including about 18 months of active enrollment.

Planned start date (first participant on study): December 2022.

The planned study termination (clinical cutoff) corresponds to the date when each participant has been followed-up for 12 months or is deceased.

End of study occurs when all of the following criteria have been satisfied:

- The trial is closed to enrollment

AND

- The last included participant has been followed for 12 months or if deceased, each participant has been followed-up for 12 months or is deceased.

23.3. DEFINITIONS OF DURATION OF STUDY PER PARTICIPANT

Depending on the period (light or dark blue on the figure 2), participants will be included either in the control arm (light blue) or in the intervention arm (dark blue). Participants will be evaluated at scheduled contact moments as described in section 7.

Each participant will be followed-up for 12 months after inclusion.

To have a real overview of the outcome of multimorbid patients, especially about survival and institutionalisation, a longer follow-up is highly relevant. Therefore, we plan to monitor patients' vital status and living situation until 5 years after inclusion. This follow-up is additional and not mandatory to fulfill our main objectives. It will be conducted only if financial support is retrieved.

Participants will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period.

Participants may withdraw their consent at any time; no further study activities will be conducted on them.

Study discontinuation occurs when an enrolled participant ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in section 7). Participants have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.

The date and reason for study discontinuation will be clearly documented in the participant's eCRF.

23.4. PROTOCOL DEVIATION

A protocol deviation is defined as any excursion from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to participant inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the participants' Informed Consent, data reporting, the responsibilities of the investigator, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might have effect on the timeframe of the trial and the validity of centre randomisation such as centre withdrawals or GerOnTe intervention implementation delay,
- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion

criteria (which could mean that the participant is not eligible for the trial) and those having an effect on participant evaluability,

- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting serious adverse events, etc.

The investigators may suggest to the Sponsor the authorisation of certain protocol deviations, especially if they are related to the inclusion/exclusion criteria or if they may have an effect on the evaluability of the participants. As a general rule, no deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorised. Protocol deviations considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

24. SELECTION OF PATIENTS

24.1. INCLUSION CRITERIA

General inclusion criteria

12. Age \geq 70 years old,
13. New or progressive cancer (breast, lung, colorectal, prostate) fulfilling the tumour specific inclusion criteria,
14. Estimated life expectancy greater than 6 months,
15. At least one moderate/severe multimorbidity inclusion criteria other than current cancer (see separate list under 5.3),
16. Patients must be willing and able to comply with study procedures,
17. Voluntarily signed and dated written informed consents prior to any study specific procedure,
18. QLQ-C30 Quality of Life Questionnaire fully completed at baseline, before inclusion.

Tumour specific inclusion criteria

19. Specific inclusion criteria for breast cancer:

19.1. Non-metastatic breast cancer (M0):

- No prior treatment for the current breast cancer.
- All 3 criteria required:
 - Clinical staging: cT2-3-4 Nany, or cTany N1-2-3,
 - The cancer specialist considers* surgery,
 - The cancer specialist considers* radiotherapy and/or chemotherapy.

19.2. Metastatic breast cancer (M1): Both criteria required:

- The cancer specialist considers* chemotherapy or PARP-inhibitors or mTOR-inhibitors / PIK3CA inhibitors; Previous endocrine therapy +/- CDK4/6 inhibitors is allowed,
- The patient received maximum 1 prior line of chemotherapy for metastatic disease.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

20. Specific inclusion criteria for colorectal cancer:

20.1. Non-metastatic colorectal cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital.
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery,
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* chemotherapy.

20.2. Metastatic colorectal cancer (M1):

- The cancer specialist considers* first line systemic therapy and/or radiotherapy (+/- surgery). No previous chemotherapy allowed except adjuvant/perioperative chemotherapy stopped for more than 12 months.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

21. Specific inclusion criteria for lung cancer:

21.1. Non-metastatic lung cancer (M0):

- No prior therapy for the current tumour in the recruiting hospital.
- At least one of the 3 criteria required:
 - The cancer specialist considers* surgery (patients considered for treatment with percutaneous thermoablation alone are not eligible),
 - The cancer specialist considers* radiotherapy (except SBRT),
 - The cancer specialist considers* systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

21.2. Metastatic lung cancer (M1):

- The cancer specialist considers* first or second line systemic therapy. Possible systemic therapies are chemotherapy and/or immune therapy and/or targeted therapy. Patients only considered* for monotherapy with anti-EGFR TKI or somatostatin analog are not eligible.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

22. Specific inclusion criteria for prostate cancer:

22.1. Non-metastatic prostate cancer (M0): one of the following:

- First diagnosis M0 prostate cancer (no therapy received yet for prostate cancer): at least one of the 2 criteria required:
 - The cancer specialist considers* radiotherapy,
 - The cancer specialist considers* hormone therapy (ADT +/- combination Abiraterone and Prednisone).
- Salvage treatment M0 prostate cancer (received prior surgery at least 6 months before):
 - The cancer specialist considers* radiotherapy (+/- ADT).
- Non-metastatic castration resistant prostate cancer:
 - The cancer specialist considers* treatment intensification (ADT + Enzalutamide or Apalutamide or Darolutamide).

22.2. Metastatic prostate cancer (M1):

- The cancer specialist considers* treatment with Abiraterone or Enzalutamide or Apalutamide, or Docetaxel or Cabazitaxel or PARP-inhibitors or Lutetium PSMA.

**‘consider’ implies that this treatment may be a treatment option for this patient in this particular setting. If at a later point, a different treatment choice is made, the patient remains eligible.*

24.2. EXCLUSION CRITERIA

2. Mental illness/cognitive impairment that limits ability to provide consent or complete trial procedures.
5. Participating to an interventional clinical trial with a non-registered anticancer drug or to another geriatric intervention trial.
6. Patients and caregivers are unable or unwilling to use ICT-devices (tablet, computer, smartphone) or the Internet according to protocol.
7. Patient already included in this study.

24.3. SEVERE MORBIDITY CRITERIA

Patient must be fulfilling one or more of the criteria below:

General

70. Two or more unscheduled comorbidity related hospitalisations in the past year (not related to index cancer).
71. Having received out-patient care from two more specialties in the past year (not related to index cancer).

Cardiac

72. Any prior symptomatic myocardial infarction.
73. Any past valve replacement, percutaneous coronary intervention), percutaneous transluminal coronary angioplasty) or coronary artery bypass graft.
74. Congestive heart failure under follow-up by a cardiologist.
75. Chronic exertional angina.
76. Regular use of anti-anginal medication.
77. Left ventricular hypertrophy.
78. Dyspnoea or activity restriction secondary to cardiac status.
79. One or more admissions to hospital for cardiac reasons in past year.

Vascular

- 80. Previous vascular intervention.
- 81. Symptomatic atherosclerotic/peripheral vascular disease.

Venous

- 82. Any history of pulmonary embolism.
- 83. Use of coumadin/warfarin, heparin, DOAC or NOAC with indication venous disease.

Hypertension

- 84. Need of three or more types of blood pressure medication.

Haematopoietic

- 85. Any chronic hematologic disease.
- 86. Haemoglobin: <10 g/dL (6.0 mmol/l) (not related to index cancer).

Endocrine

- 87. Insulin dependence.
- 88. Diabetes-related complications (retinopathy, neuropathy, nephropathy, coronary artery disease or peripheral arterial disease).
- 89. Poorly controlled diabetes mellitus or diabetic coma in the past year.
- 90. Requires adrenal hormone replacement.

Pulmonary

- 91. Dyspnoea at rest.
- 92. Limited activities secondary to pulmonary status.
- 93. Requires oral steroids for lung disease.
- 94. One or more admissions to hospital for pulmonary reasons in past year.
- 95. Two or more hospitalisations for pneumonia in past five years.

Renal

- 96. eGFR < 30 ml/min.

Hepatobiliary

- 97. Chronic hepatitis.
- 98. Cirrhosis.
- 99. Portal hypertension with moderate symptoms.
- 100. Compensated liver failure.
- 101. Clinical or lab evidence of biliary obstruction (not related to index cancer).
- 102. Acute or chronic pancreatitis or hepatitis in past 5 years.

Stomach/intestine

- 103. Recent ulcers (<6 months) or any history of ulcers requiring hospitalisation.
- 104. Any history of inflammatory bowel disease.
- 105. Any swallowing disorder or dysphagia.

- 106. Chronic diarrhoea (not related to index cancer).
- 107. Bowel impaction in the past year (not related to index cancer).
- 108. Status post bowel obstruction (not related to index cancer).
- 109. Ostomy/stoma in situ (not related to index cancer).

Nutrition and weight

- 110. Weight loss more than 6 kg in past six months.
- 111. Weight loss more than 3 kg in past 1 month.
- 112. Significantly decreased food intake.
- 113. Body mass index < 19 kg/m².
- 114. Body mass index > 38 kg/m².

Neurologic

- 115. Status post cerebrovascular accident (CVA) with at least mild residual dysfunction.
- 116. Any past central nervous system neurosurgical procedure.
- 117. Neurodegenerative disease including Parkinson's disease, parkinsonism, multiple sclerosis, myasthenia gravis etc.).
- 118. Requires daily meds for chronic headaches or headaches that regularly interfere with daily activities.

Sensory

- 119. Partially or functionally blind, unable to read newsprint.
- 120. Functional deafness or conversational hearing impaired despite hearing aid.
- 121. Laryngectomy.

Mobility

- 122. Requires a walking aid/wheelchair.
- 123. Difficulties in activities of daily living secondary to mobility impairment.
- 124. Difficulty walking >100m without resting.
- 125. Requires steroids or immunosuppressant medication for arthritic condition or connective tissue disease.
- 126. Prior or current symptomatic vertebral compression fractures from osteoporosis.

Psychiatric

- 127. Active substance abuse with social, behavioural or medical complications.
- 128. History of schizophrenia or another psychotic disorder.
- 129. Requires daily antipsychotic medication.
- 130. Current usage of daily anti-anxiety medication.
- 131. Currently meets DSM criteria for major depression or bipolar disorder.
- 132. One or more episodes of major depression in the past 10 years.
- 133. Any previous psychiatric hospitalisation.

Cognition/Delirium

- 134. One or more prior deliriums in the past 10 years.
- 135. Cognitive impairment that does not inhibit patient to provide informed consent and understand study procedures.

Previous cancer

- 136. Another type of cancer than the index cancer with at least one of the following criteria:
 - Required chemotherapy or radiation therapy in the past 5 years,
 - Non-curable and/or metastatic cancer.

Instrumental Activities of Daily Living (iADL)

- 137. Care dependent in one or more aspects of the following instrumental activities of daily living (preparing meals, walking outside alone, managing medication).

Social

- 138. Patients has no or very limited support system or informal caregivers.

25. STUDY INTERVENTION GERONTE-SYSTEM

25.1. INTERVENTION DESCRIPTION

The intervention will include the following components, which will be elaborated on in sections 6.2 to 6.6 and figures 3 and 4.

- A health professional consortium (HPC) for each patient, which will work together to make recommendations regarding oncologic treatment and non-oncologic interventions, at baseline and in the course of treatment. This will be in addition to the usual multidisciplinary tumour board (MTB) which will provide an oncologic treatment recommendation based on the usual oncologic work-up.
- An advance practice nurse (APN) as case-manager, who will be the primary contact person for the patient during the oncologic treatment and subsequent follow-up.
- A baseline patient evaluation consisting of a comprehensive geriatric assessment (CGA) by a geriatrician, APN or trained study collaborator, which will focus on general health status, comorbidities and intrinsic capacity. Baseline documentation of patient preferences and priorities will be collected by the APN.
- A health care professional dashboard, called Holis Dashboard, which 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 the standard consensus dataset. Dashboard data will be made available selectively to all health care professionals of the HPC.

- A patient monitoring application called Holis Patient App, which will allow for monitoring of symptoms and signs of destabilised comorbidity or functional decline during and after treatment, with additional self-management library with recommendations for how the patient can deal with issues or for contacting their health care professionals in case of symptoms requiring urgent intervention.
- Additional data (paper questionnaires and test) will be collected every 3 months and are listed under sections 7.2 and 7.3.

25.2. HEALTH PROFESSIONAL CONSORTIUM (HPC)

For each patient, a HPC is constructed based on the needs of the specific setting of the patient, but at minimum consists of a cancer specialist, a geriatrician and an APN. Additional input from other health care professionals, including the general practitioner, will be gathered by the APN prior to HPC meetings if these professionals are not able to join the HPC themselves. In brief, the HPC meets before the final treatment decision is made with the patient. The first HPC takes place within 15 days of inclusion. At 3, 6, 9 and 12 months (+/- 15 days), there are fixed follow-up meetings, but additional HPC meetings can be planned as needed in case of changes in the patient situation. The APN is responsible for the coordination of the HPC meetings.

25.3. MULTIDISCIPLINARY TUMOUR BOARD (MTB)

The MTB will be executed as per standard of care for each hospital.

25.4. ADVANCE PRACTICE NURSE (APN)

The advance practice nurse will play a central role in the care for the older patients with multimorbidity and cancer. The APN will do the inclusion for the clinical trial during the intervention phase, will collect additional information regarding patient's social situation, priorities and preferences, will organize the HPC meetings at regular intervals, will monitor patients during treatment based on the Holis Patient App and will initiate non-oncologic interventions based on the recommendations of the HPC.

25.5. HOLIS DASHBOARD DESCRIPTION AND FUNCTIONALITIES

The components of the decision making Holis Dashboard include:

- An image of the patient,
- Personal data (including primary care giver and general practitioner information),
- Information about the living and social situation,
- Minimal oncological dataset,
- Information about comorbidities including severity and impact on daily life,
- Information about prognosis (non-cancer related),
- Intrinsic capacity evaluation (defined by the WHO as the description of all the individual-level attributes that might contribute to healthy aging) by the geriatrician,
- Patient priorities and preferences,
- Decision control preferences evaluated by the patient,
- Information about medication and allergies,
- Input from other health care professionals,
- Decision making checklist and report (standardised form).

The components of the follow-up dashboard additionally include:

- Symptom monitoring information from the Holis Patient App,

- Questions from the patient to the APN or HPC,
- Treatments (oncological and non-oncological) and hospitalisations,
- Overview of past and future HPC-meetings.

The data will be completed on the Holis Dashboard via a secured external website accessible by health care professionals with access codes.

Additional functionalities include reminders for planning HPC meetings and for incomplete data.

25.6. HOLIS PATIENT APP DESCRIPTION AND FUNCTIONALITIES

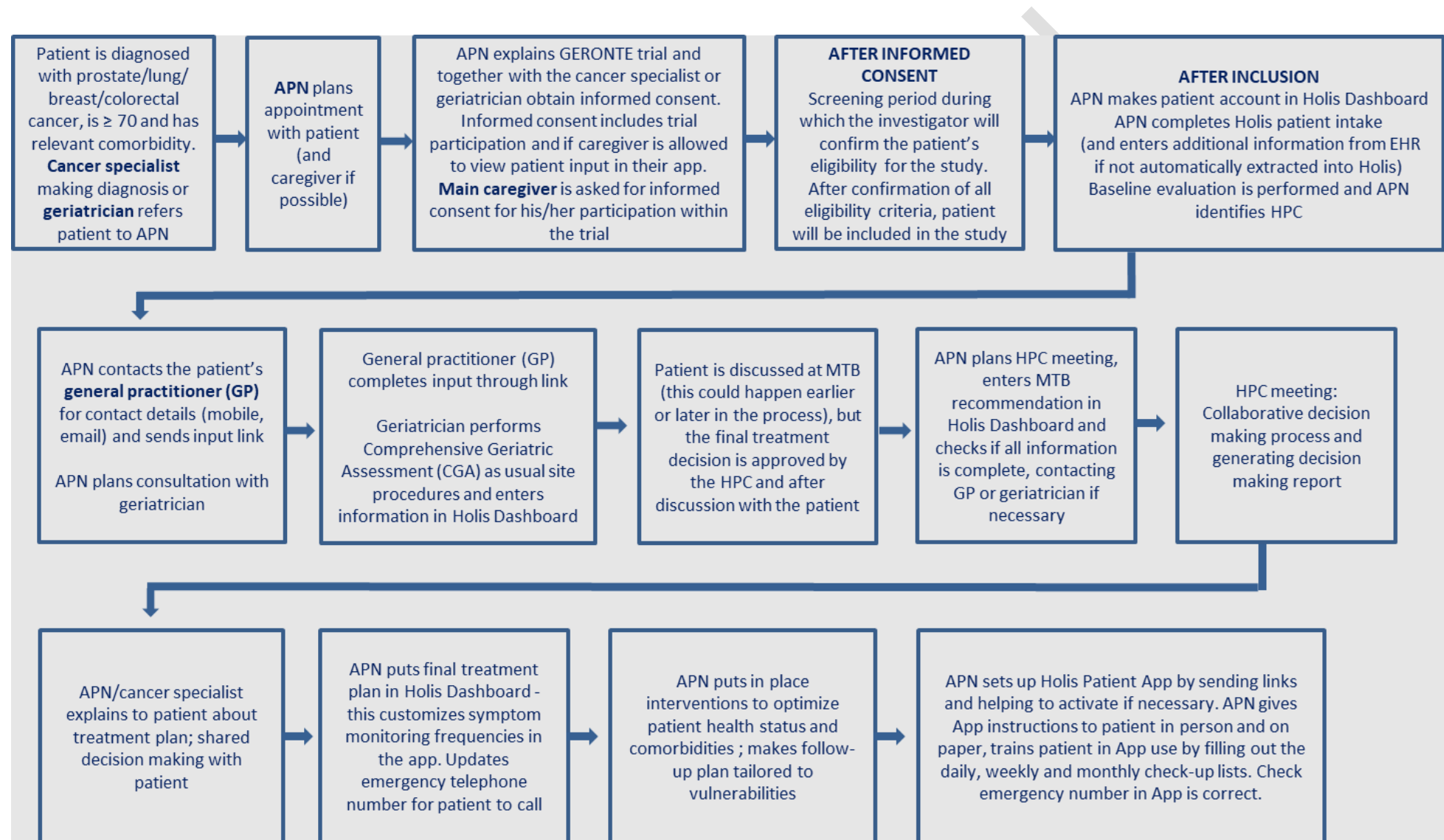
The components of the Holis Patient App are:

- Symptom monitoring tailored to the tumour type and treatment,
- 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,
- Space for personal notes,
- And the possibility to set up reminders for completing the symptom monitoring.

Holis Patient App can be installed on following ICT-devices: smartphone, digital tablet, computer (windows and apple).

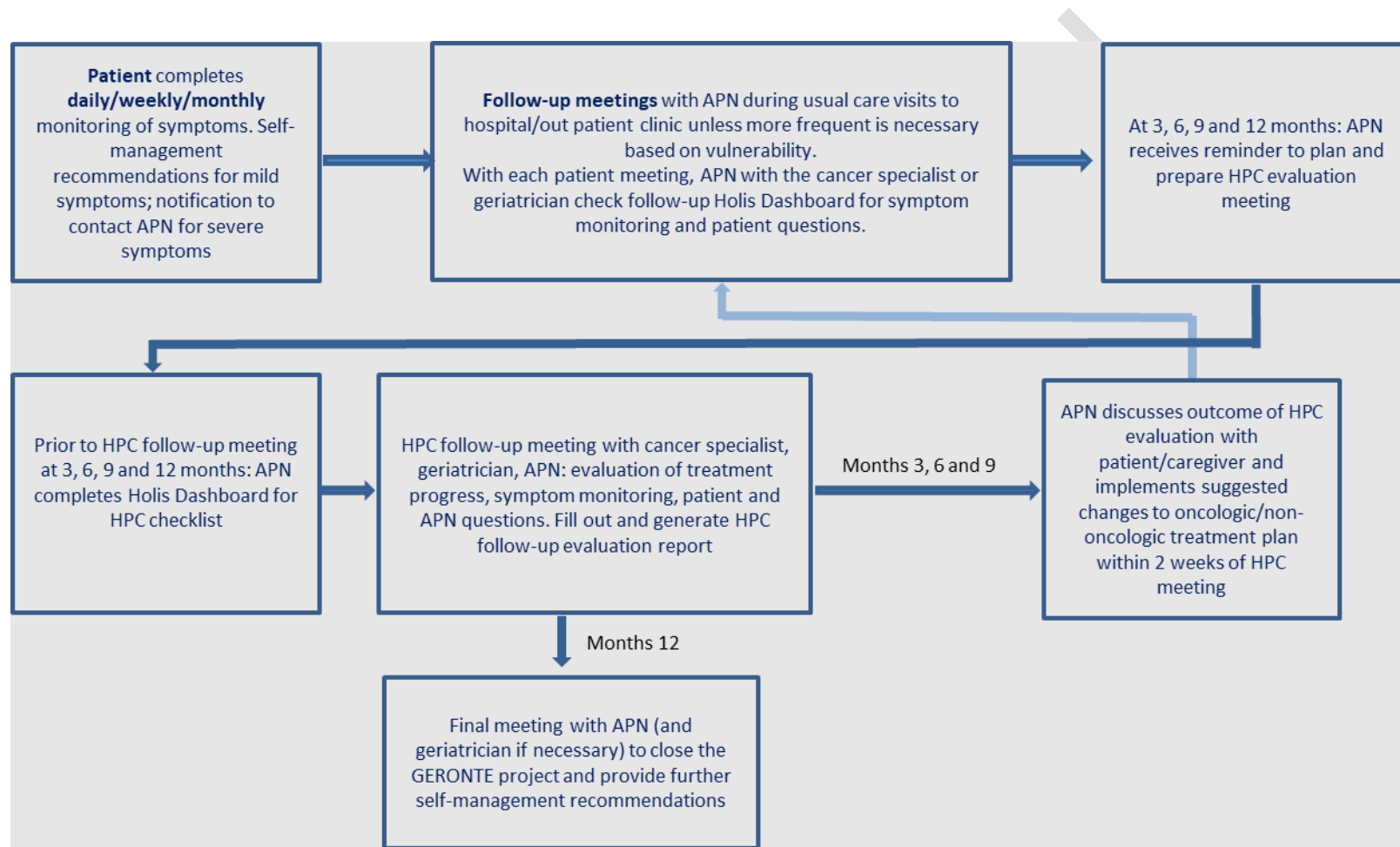
For patients without ICT-device (estimated to 10% of the patients) in order to avoid discrimination, a digital tablet will be provided for the duration of the study (with Holis Patient App installed and WIFI internet subscription when necessary).

Figure 3 : For intervention arm: inclusion and decision making



CONFIDENTIAL

Figure 4 : For intervention arm: during and after treatment



26. PATIENTS' MANAGEMENT

26.1. DEFINITION OF SPECIFIC STUDY TERMS

26.1.1. Study collaborators

Study collaborators will conduct patient assessments.

Study collaborators include clinical research assistants, nurses and any health care professional involved in the study.

Medical assessments will be performed by health care professionals (cancer specialist, geriatrician, nurse...).

Self-questionnaires will be given to the patient by a study collaborator (most often by a clinical research assistant, nurse and according to the habits of each site).

Other questionnaires and tests will be conducted by a study collaborator (most often by a health care professional or a study collaborator and according to the habits of each site).

26.1.2. Patient's caregiver

The informal caregiver is a person who provides assistance to a dependent and/or disabled person, generally part of their close circle of the patient (family member such as spouse or husband, ascendants, descendants, etc.) or a person that the patient has chosen (with a close and stable relationship with the person being cared for). The help provided is non-professional.

At the beginning of the study, the patient will be asked to identify his or her informal caregiver. If there is more than one, he/she will choose a primary caregiver for the study.

26.1.3. Institutionalisation

Institutionalisation means that a patient moves permanently to an institution among which are considered retirement houses.

26.1.4. Unscheduled hospitalisation

Unscheduled hospitalisation includes any hospitalisation which has not been previously planned because of an unscheduled event (severe adverse event, complication of treatment, decompensation of morbidity) whatever it is linked or not to the emergency room.

26.2. CONTROL ARM EVALUATIONS

	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)
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 scale)**		X	X	X	X	X
Anxiety and depression scale (HADS)*		X	X	X	X	X
Patient Caregiver Information**		X	X	X	X	X
Worth of treatment*				X		X
Unscheduled hospitalisations**	<-----X----->					
Patient institutionalisation**	<-----X----->					
Patient experience (P3CEQ)*				X		X
Intention to use (Modified version of MAUQ)*				X		X
Resource use (direct and indirect costs) */**		X	X	X	X	X
Ancillary studies**	<-----X----->					

* Self-administrated questionnaires

** Questionnaires and tests conducted by a study collaborator

26.2.1. Screening evaluation and informed consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. During the screening period and before inclusion, the Investigator will confirm the participant's eligibility for the study. The screening period will not exceed 28 days.

26.2.2. Baseline assessment

After confirmation of all eligibility criteria and upon request, eligible participants will be included in the study centrally at the KU Leuven/UZ Leuven as described in a specific SOP provided by the Sponsor.

The baseline period is accepted within a week between informed consent and inclusion.

The following assessments will be done:

- Medical history, baseline condition including comorbidities (*conducted by a study collaborator*),
- Assessment of baseline signs and symptoms (*conducted by a study collaborator*),
- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Concomitant treatments (number only) (*conducted by a study collaborator*),
- Demographic data (i.e. sex, age, height and weight) (*declared by the patient*),
- Cancer information (*conducted by a study collaborator*):
 - Date of diagnosis of the primary disease,
 - Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), if applicable,
 - Current cancer characteristics and treatments,
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Patient institutionalisation (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver (link with the patient, date of birth and initials) (*conducted by a study collaborator*),
- Collection of information regarding resource use (informal caregiver, home support, transport) (as listed under Section 10).

26.2.3. Patient management and follow-up

Each patient will be followed up to 12 months.

Every 3 months during one year, the following assessments will be done:

- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Demographic data (only weight) (*declared by the patient*),
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Cancer information (current cancer characteristics and treatments) (*conducted by a study collaborator*),
- Patient institutionalisation (*conducted by a study collaborator*),
- Unscheduled hospitalisations (date, reason and location) (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver: same since baseline or change (*conducted*

by a study collaborator).

- Patient-reported overall experience (Person-Centred Coordinated Care Experience Questionnaire-P3CEQ, appendix 10) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Worth of treatment only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Intention to use: mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (appendix 11B) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Resource use (direct/indirect costs) as listed under section 10 (*patient self-administrated paper questionnaire*),
- Ancillary studies: please refer to appendix 1.

In case of **study discontinuation**, the date and reason of will be recorded on the participant's CRF.

Participants who **withdraw consent** will not be followed with any study procedures.

26.2.4. End of participation

At the end of the 12 months of the GerOnTe intervention implementation, a study collaborator will inform the patients of their end of participation.

26.3. INTERVENTION ARM EVALUATIONS

	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)
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
APN consultation + assessments		X				
CGA (Comprehensive Geriatric Assessment as usual site procedures)**		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 scale)**		X	X	X	X	X
Anxiety and depression scale (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----->				
Holis Patient App completion*		<-----X----->				
Patient experience (P3CEQ)*				X		X
Intention to use (Modified version of MAUQ)*				X		X
Resource use (direct and indirect costs) */**		X	X	X	X	X
Ancillary studies**		<-----X----->				

* Self-administrated questionnaires

** Questionnaires and tests conducted by a study collaborator

26.3.1. Screening evaluation and informed consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. During the screening period and before inclusion, the Investigator will confirm the participant's eligibility for the study. The screening period will not exceed 28 days.

26.3.2. Baseline assessment

After confirmation of all eligibility criteria and upon request, eligible participants will be included in the study centrally at the KU Leuven/UZ Leuven as described in a specific SOP provided by the Sponsor.

The baseline period is accepted within a week between informed consent and inclusion.

The following assessments will be done:

- Medical history, baseline condition including comorbidities (*conducted by a study collaborator*),
- Assessment of baseline signs and symptoms (*conducted by a study collaborator*),
- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Concomitant treatments (number only) (*conducted by a study collaborator*),
- Demographic data (i.e. sex, age, height and weight) (*declared by the patient*),
- Cancer information (*conducted by a study collaborator*):

- Date of diagnosis of the primary disease,
- Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), if applicable,
- Current cancer characteristics and treatments,
- APN consultation and assessments (*see section 7.3.3.*),
- CGA (Comprehensive Geriatric Assessment as usual site procedures) assessing **general health status, intrinsic capacity, documentation of patient preferences, and oncological work-up (MTB)** (*conducted by a study collaborator*),
- Quality of life (EORTC QLQ-C30, appendix 2) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),
- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Patient institutionalization (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical frailty scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's main caregiver (link with the patient, date of birth and initials) (*conducted by a study collaborator*),
- Collection of information about the patient's general practitioner (contact details to send input link) (*conducted by a study collaborator*),
- Collection of information regarding resource use (informal caregiver, home support, transport) as listed under section 10.

26.3.3. APN consultations and assessments

APN first contact

The aim of this first contact between APN and patient, and caregiver if possible, is to identify the HPC (including APN, geriatrician, oncologist, general practitioner (GP), home-based nurse, specialists according to other coexisting diseases and supportive care professionals), to train patients and caregivers on Holis Patient App usage and to upload patient's treatment preferences in the Holis Dashboard.

APN consultation and assessments in collaboration with a physician as needed

- For patient and caregiver,
- Outlining multimorbidity-informed treatment decision (and possible patient access to data through the Holis Patient App),
- Training in Holis Patient App usage,
- Advising on self-management when intrinsic capacity allows it,
- Collecting contact information of the patient's general practitioner and send him/her the link to complete information.

26.3.4. Patient management and follow-up

Each patient will be followed up to 12 months.

Every 3 months during one year, the following assessments will be done:

- Performance status (ECOG-PS, appendix 6) (*conducted by a study collaborator*),
- Demographic data (only weight) (*declared by the patient*),
- Quality of life (EORTC QLQ-C30, appendix 3) (*patient self-administrated paper questionnaire*),
- Quality of life (EORTC QLQ-ELD14, appendix 3) (*patient self-administrated paper questionnaire*),

- Overall health status (EQ-5D-5L, appendix 8) (*patient self-administrated paper questionnaire*),
- Cancer information (current cancer characteristics and treatments) (*conducted by a study collaborator*),
- Patient institutionalization (*conducted by a study collaborator*),
- Unscheduled hospitalisations (date, reason and location) (*conducted by a study collaborator*),
- Autonomy (Katz ADL) (appendix 4) (*conducted by a study collaborator*),
- Anxiety and depression (HADS, appendix 7) (*patient self-administrated paper questionnaire*),
- Chair stand test (*conducted by a study collaborator*),
- Clinical Frailty Scale (appendix 5) (*conducted by a study collaborator*),
- Collection of information about the patient's caregiver: same since baseline or change (*conducted by a study collaborator*).
- Patient-reported overall experience (Person-Centred Coordinated Care Experience Questionnaire-P3CEQ, appendix 10) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Worth of treatment only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Intention to use: mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version) (appendix 11A) only at 6 and 12 months (*patient self-administrated paper questionnaire*),
- Ancillary studies: please refer to appendix 1.

Collection of symptoms and adverse events on Holis Patient App

- Frequency varies depending on the symptom and the treatment between daily, weekly and monthly.
- Registration of hospitalisations in the web-based Holis Dashboard.

The patient will receive:

- self-management advice based on their symptom reporting,
- emergency contact details and prompts to call a medical team member for specific symptomatic treatment depending on severity.

The data are centralised in Holis Dashboard and used for subsequent actions.

In case of **study discontinuation**, the date and reason of will be recorded on the participant's eCRF.

Participants who **withdraw consent** will not be followed with any study procedures.

26.3.5. End of participation – end of GerOnTe intervention implementation

At the end of the 12 months of the GerOnTe intervention implementation, a study collaborator (mostly the APN) will inform the patients of their end of participation. She/he will also proceed to the remote uninstallation of the application as soon as possible.

In case of a tablet loan, the APN will also organize the return of the equipment.

In the event of the patient's death occurs before 12 months and within one month of the death, the APN will contact the family again in order to remotely uninstall the application. In case of a tablet loan, the APN will also organize the return of the equipment.

26.4. EARLY DISCONTINUATION OF THE STUDY

In case of early closure of the research, inclusions will be definitely stopped but, as defined in section 4.2, end of study will occur when all patients have stopped study procedure and the last included patient has been followed for 12 months or if deceased, each participant has been followed-up for 12 months or is deceased.

26.5. SPECIAL SITUATIONS DURING THE STUDY

It is important to note that the following situations do not result in the patient's discontinuation of the study:

- Progression of the disease,
- Change of treatment line.

Visits and assessments should be maintained as per protocol.

27. CAREGIVER'S MANAGEMENT

Written informed consent for the primary caregiver's participation in the study must be obtained prior to conducting any study-specific questionnaires.

Primary caregiver may be involved in three different ways:

- For all caregivers:
 - Zarit burden interview (ZBI, appendix 9) to evaluate the caregiver burden (caregiver *self-administrated paper questionnaire*),
 - Questionnaire for the measurement, evaluation and estimation of costs of informal care.
- For a sample of caregivers: the ancillary study (appendix 1).

For both control and intervention arms, all main caregivers will be asked to complete the Zarit burden interview through paper questionnaires, and the questionnaire for the measurement, valuation and estimation of costs of informal care at baseline, 3, 6, 9 and 12 months after inclusion.

28. PHYSICIAN AND HEALTH CARE PROFESSIONALS' MANAGEMENT

Written informed consent for the physician and health care professionals' participation in the study must be obtained prior to conducting any study-specific questionnaires.

Physician and health care professionals may be involved in two different ways:

- For all physician and health care professionals in the HPC: MAUQ questionnaire (appendix 12) to evaluate physician and health-care-professionals-reported overall satisfaction with the application of the GerOnTe intervention (physician and health care professional *self-administrated paper questionnaire*).
- For a sample of physician and health care professionals: the ancillary study (appendix 1).

Physicians and health professionals in the HPC will be asked to complete the adjusted version of the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Provider version). The questionnaire will be administered through paper questionnaire at 6 and 12 months after inclusion of the first intervention arm patient.

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29. RESOURCE USE MANAGEMENT

To perform the economic evaluation, we will collect total costs, which are broken down into direct costs, either medical or non-medical, and indirect costs. These resource data will be collected for both control arm and intervention arm.

Resource use data will be collected until 12 months post-inclusion in the trial through different sources:

- Trial case report forms (CRFs) completed by the study collaborator or the APN every three months,
- Electronic medical records (EMRs) and electronic patient files linked to the patient sample by deterministic matching,
- Patient questionnaires (e.g., patient report the frequency of visits to the medical specialist, APN, general practitioner),
- Questionnaire/interview for cost outside the clinical site, direct non-medical costs and indirect costs.

Resource use data, questionnaires and interviews will be completed at baseline and at 3, 6, 9 and 12 months. A three-month interval is a suitable time for minimizing recall bias and the questionnaire burden.

Direct medical costs related to intervention (for intervention arm only) will be collected using TDABC methodology and Business case / estimates (for intervention).

All resource use will be valued in monetary terms using appropriate unit costs or participant valuations estimated at the time the trial starts.

Category	Resources
Direct medical costs	
Hospital-based services	Hospitalisations, medical goods, procedures
Pharmaceutical consumptions	Medicinal products, medicinal devices
Personnel	Medical time, APN time, MTB time, other
Emergency department	Unscheduled visits to the emergency room, procedures performed, use of ambulance, other
Outpatient care	Medical consultations, medical imaging, other
Intervention (for intervention arm only)	Training, equipment, MTB time, other
Direct non-medical costs	
<ul style="list-style-type: none"> • Travel expenses • Community care/formal care 	
Indirect costs	
<ul style="list-style-type: none"> • Caregiver productivity loss • Unpaid caregivers' labour (informal care) 	

Synthesis for patient questionnaires at baseline and at 3, 6, 9 and 12 months:

- Hospitalisations if outside the clinical site,
- Procedures (e.g. surgery, medical imaging) if outside the clinical site,
- Unscheduled visits to the emergency room,
- Medical consultations (e.g. visit to GP, psychologist, nurse),
- Travel expenses (e.g. taxis, personal vehicles, public transports, etc),
- Community care/formal care (e.g. home help)

Synthesis for caregiver questionnaire at baseline and at 3, 6, 9 and 12 months:

- Caregiver productivity loss (e.g. how many hours did the caregiver miss from work due to relative's disease or condition),
- Unpaid informal care (e.g. time spent on household activities or unpaid activities).

Synthesis concerning the data collection performed by the study collaborator for the clinical site (information that concern only the clinical site and if possible, other services than oncology):

- Hospitalisations (e.g., reason for hospitalisation, bed-days, length of stay),
- Procedures (e.g., surgery, medical imaging),
- Medicinal products (e.g., drugs, medical devices),
- Unscheduled visits to the emergency room.

30. STATISTICAL CONSIDERATIONS**30.1. HYPOTHESES AND NUMBER OF PARTICIPANTS NEEDED**

Sample size calculations were drawn in order to be able to detect a mean difference of 10 points or more (on a score from 0 to 100) (Osoba 1998), should the intervention be effective, for at least one of the three targeted health-related quality of life (HRQoL) scores (common standard deviation of 20 points). Each of the three scales will be independently tested. If the GerOnTe intervention improves at least one of the three scores by at least 10 points, the intervention is considered effective. If the GerOnTe intervention improves one of the 3 subscores by 10 or more points and decrease another subscore by 10 or more points, the intervention will be considered effective. In that unlikely situation, the GerOnTe scientific committee will conduct and communicate a clinical analysis and clinical interpretation.

With a 1.6% two-sided type I error and a statistical power of 90%, the minimum number of patients to include is 222. Accounting for a possible 20% dropouts, the total minimum number of patients to be included is 278. 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 corresponding to 10 patients on average per step and per centre (Table 2.1)

Randomized investigating sites	Number of patients to include per step	Total Nb of patients to include control arm	Total Nb of patients to include Intervention arm	Total nb 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

Table 1: Number of patients who will be included in the control and intervention arm for each of the eight investigating sites. 10 patients will be included per step.

Definition of study populations

- Total population: All participants included.

- Eligible population: All participants included without major violation of eligibility criteria.
- Intention to treat population: All patients will be included in the analysis in the group in which they were initially randomised and all their data will be used.
- Per protocol population: Only patients who are strictly compliant with the procedure will be included (Lost-of-follow-up will be, in particular, excluded).

30.2. STATISTICAL ANALYSIS

30.2.1. Analysis strategy

An intention-to-treat analysis with replacement of missing data by multiple imputation will be performed as the principal analysis. To check the robustness of the results of the ITT analysis, sensitivity analysis will be performed.

A per protocol analysis on available data could be carried out a second time.

Descriptive analysis will always be presented overall and by treatment group.

Comparative analysis between procedure groups will be systematically performed. All comparisons will be performed with a type I error of 5%.

30.2.2. Statistical methods

Qualitative variables will be described by numbers and percentage.

Quantitative variables will be described by numbers, mean, standard deviation, median, range, and interquartile range.

We will attempt as much as possible to associate a graphic representation of the analyses.

Statistical analyses will be performed with the SAS® software (version 9.4) and R software according on the type of analysis.

30.2.3. Analysis plan

Description of the inclusions and follow up

The description of the number of inclusions per site and per step will be performed, globally and per group (before and after the implementation of the GerOnTe intervention).

Patients included in the analysis

Only the patients presenting at least one of the following conditions can be excluded from the analysis:

- patients wrongly included for unsigned consent,
- patients wrongly included for major non-respected eligibility criteria,
- patients who withdrew their informed consent.

The Trial Steering Committee (TSC) will make this decision of exclusion after documentation of observations by clinical trial statistical team at EUCLID, blinded to the procedure group and to the patient's evolution after inclusion.

Except for these exclusions, the patients who die, are lost to follow-up or leave the study, will all be included in the analysis.

Baseline characteristics

The following variables will be described:

- respect of the eligibility criteria,
- centres characteristics,
- patients clinical, socio-economic and socio-demographic characteristics.

Analysis of primary endpoint

The primary endpoint is the Quality of Life assessed by the EORTC QLQ-C30 (version 3.0) questionnaire at 6 months after GerOnTe implementation. It has 3 sub-scores that will be analyzed independently, with alpha risk adjustment.

In order to take into account the stepped wedge study design and its specificities (possible temporal effect, variable cluster size, presence of clusters), generalized mixed linear models will be used (Husset & Hughes 2007). Since the variables to be explained are quantitative (normalized scores), mixed linear regression models will be used. Random effects on the site, the time and the time of measurement (before/after the intervention is implemented) will be introduced where possible. The multiplicity of tests will be taken into account by adjusting the p-value using a Family-wise error rate method (Burman Stat Med 2009).

Analysis of secondary endpoints

- Quality of life assessed by the EORTC QLQ-C30 (version 3.0) and ELD 14.
 - The endpoints of quality of life will be analyzed in exactly the same approach as the primary endpoint.
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Survival
 - Depending on the event of interest, frailty models, nested frailty models or joint nested frailty models will be used.
- Patient autonomy assessed at 3, 6, 9 and 12 months:
 - By the Katz ADL questionnaire: the dependence score will be analyzed with a mixed linear regression model (with the same approach as the primary endpoint). A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
 - The proportion of patients living at home 6 months after inclusion will be analyzed with a mixed logistic regression model (with the same approach as the primary endpoint).
 - The number of completed chair stands in 30 seconds (Chair stand test) will be analyzed with a mixed linear or logistic regression model (with the same approach as the primary endpoint and depending on the distribution of the number of chair stands).
 - The frailty score and the grade of performance status (ECOG-PS) will be analyzed with a mixed logistic regression model (with the same approach as the primary endpoint).
 - Weight will be analyzed with a mixed logistic or linear regression model depending on the distribution of both variables (with the same approach as the primary endpoint).
- Patient anxiety assessed by the HADS at 3, 6, 9 and 12 months
 - These endpoints will be analyzed each with a mixed linear or logistic regression model depending on the distribution of the scores (with the same approach as the primary endpoint).
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Patient institutionalisation
 - The proportion of patients in nursing home at 6 and 12 months after inclusion will be analysed with a mixed logistic regression model (with the same approach as the primary endpoint).

- Unscheduled hospitalisations collected until 12 months
 - Depending on the event of interest, frailty models, nested frailty models or joint nested frailty models will be used.
- Cost-effectiveness and cost-utility analysis:
 - The economic evaluation will be conducted from a societal perspective, which accounts both the costs in the public payer perspective and other direct and indirect costs relevant for different stakeholders, including patients (e.g., transportation, formal and informal caregiver time and/or work leave, out-of-pocket expenses, or co-payments). A secondary analysis will additionally be conducted from the payer perspective only, with the aim to estimate the budgetary impact on public finances. In this case, only the resource used within the hospital setting will be considered (e.g., direct medical costs, drugs and medications, bed-days, outpatient visits, ED visits).
 - Costs will be calculated considering resource use at patient level and unit costs of each product/service used in the care pathway. Specifically, the process of calculating the full costs will be broken down into the following three connected tasks:
 - the collection of service usage data for individual patients over a defined period;
 - the costing or pricing of each service used; and
 - the combination of these two sets of information in order to calculate the cost of the full care packages

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 available sources. A map of available patient-level RWD (Real World Data) in each country will be created to generate real-world evidence.

Time spent will be measured by microcosting.

The full economic evaluation and any analyses of the study costs and outcomes will be carried out according to the “intention to treat” (ITT) 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 analyzed 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 analysis a standard discount rate of 3% per year will be applied to both healthcare costs and outcomes.

More details on the analysis plan for the economic evaluation in the protocol for economic evaluation:

- Caregiver burden assessed by the Zarit burden interview
 - This endpoint will be analyzed with a mixed linear regression model (with the same approach as the primary endpoint).
 - A model taking into account the 4 follow-up times (3, 6, 9, 12 months) can be made by adding a random effect on the patient.
- Patient reported overall experience of person-centred coordinate care approach assessed by the P3CEQ at 6 and 12 months and qualitative analysis conducted by a health sociologist (see Ancillary study). This endpoint will be analyzed with a mixed logistic regression model since the variable are qualitative (with the same approach as the primary endpoint).
- Patient, physician and health-care-professionals-reported overall satisfaction and usability with the application of the GerOnTe intervention will be assessed by the MAUQ
 - Mixed linear regression models, allowing to take into account the centre effect but without taking into account the stepped wedge study design, will be used.
- GerOnTe patient-centred intervention implementation and usage
 - Mixed linear regression models, allowing to take into account the centre effect but without taking into account the stepped wedge study design, will be used.

31. MANAGEMENT OF ADVERSE EVENTS / SIDE EFFECTS / INCIDENTS

31.1. DEFINITIONS

The definitions and reporting requirements adopted in this protocol are based on the ISO 14155:2011 standard and according to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR) and Medical Device Coordination Group (MDCG) 2020-10/1.

31.1.1. Adverse Event (AE) (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

Note:

- This definition includes events related that are anticipated as well as unanticipated events.
- This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

31.1.2. User (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

Any healthcare professional or lay person who uses a device.

31.1.3. Serious Adverse Events (SAE) (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

A SAE is an adverse event that led to any of the following:

- Death,
- Serious deterioration in the health of the subject, that resulted in any of the following:
 - life-threatening illness or injury,
 - permanent impairment of a body structure or a body function,
 - hospitalisation or prolongation of patient hospitalisation,
 - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - chronic disease,
- Foetal distress, foetal death or a congenital physical or mental impairment or birth defect

31.1.4. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

31.1.5. Device Deficiency (DD)

A DD is an inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

31.1.6. Unanticipated Serious Adverse Device Effect (USADE)

An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered as Serious Adverse Device Effects. A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

31.1.7. SERIOUS PUBLIC HEALTH THREAT (Chapter I Article 2 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR))

An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

31.1.8. SEVERITY GRADE

Severity grade for adverse events will be based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Grade 1: the degree / extent / intensity of the event is mild (no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)

Grade 2: the degree / extent / intensity of the event is moderate (minimal intervention; local intervention; noninvasive intervention)

Grade 3: the degree / extent / intensity of the event is severe and undesirable (significant symptoms requiring hospitalisation or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: the degree / extent / intensity of the event is life-threatening or disabling

Grade 5: Death related to Adverse Event.

31.1.9. CAUSALITY ASSESSMENT

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

5. Not related
6. Possible
7. Probable
8. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

31.2. INVESTIGATOR'S RESPONSIBILITIES IN CASE OF ADVERSE EVENT / SERIOUS ADVERSE EVENT / DEVICE DEFICIENCY / NEW INFORMATION AND OTHER EVENTS

Upon signing the consent form, the investigator is responsible for collecting all adverse events and device deficiencies. He reports all serious and non-serious adverse events as well as device deficiencies that could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favorable, occurring during the use of the Holis Dashboard or the Holis Patient App. For example: wrong information provided to the patient (Holis Patient App).

The reporting period is defined as follows:

- From the date of signing the consent,
- For the duration of the patient's planned follow-up in the research,
- Until 30 days after the end of the participant's follow-up planned by the research, when it is likely to be due to the research.

The investigator reports any inadequacy in the identity, quality, durability, reliability, safety or performance of the investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer, in the SAE and Device deficiency case report form.

As the TWOBE study is a streamlined Geriatric and Oncological evaluation based on ICT for holistic patient-oriented healthcare management, no research-related AE and SAEs are expected.

The following situations should not be reported immediately to the sponsor but should be reported and documented by the investigator in the CRF:

- All non-research related events (i.e., disease progression, death...),
- Any admission for social or administrative reasons, in the absence of an adverse event,
- Any hospitalisation for medical or surgical treatment scheduled before the research; any pre-planned surgery or medical treatment must be recorded in the patient file.

AE and SAE related to cancer treatments should not be reported.

31.2.1. NOTIFICATION WITHOUT DELAY OF SERIOUS ADVERSE EVENTS AND, DEVICE DEFICIENCY AND NEW INFORMATION

The investigator assesses each adverse event in terms of its severity and each device deficiency in terms of its potential to result in an SAE if appropriate measures or intervention were not taken, or if the circumstances were less favorable.

The investigator shall notify any SAE or device deficiency that might have led to a serious adverse event to the sponsor, immediately, and **no more than 3 calendar days** from the day he/she becomes aware of it, occurring:

- from the date of signing the consent,
- during the entire duration of the patient's follow-up under the clinical investigation,
- until 30 days after the end of the participant's follow-up planned by the clinical investigation,
- using the AE/SAE form for notification of the study team to the sponsor (appendix 13).
- using the DD form for notification of the study team to the sponsor (appendix 14).
- using the SAE/DD form for notification of the sponsor to the CA's³.

If an authorized investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the sponsor by a health care professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

If the investigator becomes aware of a serious adverse event, suspected to be causally related to the clinical investigation, occurring after the end of the clinical trial, he will inform the sponsor without delay.

31.2.2. Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). The sponsor will notify all deaths as soon as possible after becoming aware to the EC and provide additional information if requested.

31.3. DECLARATION BY THE SPONSOR OF SERIOUS ADVERSE REACTIONS, DEVICE DEFICIENCY, NEW INFORMATION AND OTHER EVENTS

The investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the sponsor in accordance with instructions provided above.

The sponsor will promptly evaluate all SAEs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to investigators, ECs and applicable CA's based on applicable legislation.

³ The SAE report form in excel format can be downloaded from the following web page:

https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

31.3.1. Sponsor's reporting of Serious Adverse Events and Device Deficiencies

In accordance with article 80 (2) Regulation (EU) 2017/745 – Medical device regulation, the sponsor shall declare (via EUDAMED as soon as it is fully functional or via the Medical Device Coordination Group (MDCG) Report Form: MDCG 2020-10/2 Clinical Investigation Summary Safety Report Form v1.0) to all the national competent authorities where the clinical investigation is authorised to start:

4. Any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
 5. Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
 6. Any new findings in relation to any event referred to in points 1 and 2.
- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes deaths. Follow-up: Immediately, but not later than 2 calendar days after awareness by sponsor
 - Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event. Follow-up: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor.

The sponsor shall declare any new information that arises during the research to the CA's of participating countries and to Ethics Committee(s) when applicable, as required by European regulation.

The sponsor and the investigator shall take the appropriate urgent measures.

31.3.2. Annual reporting

The Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's and CA's containing an overview of all SADEs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

31.3.3. Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	Non-serious AE	e-CRF	Sponsor	NA
	SAE/DD	Initial SAE/DD form + follow up if necessary	Sponsor	Asap, but no later than 3 calendar days after awareness
	Death	SAE form	Sponsor	Asap
	New information	Written report	Sponsor	Asap
Sponsor	All reportable events (of all participating sites)	EU SAE report form (excel) ⁴	<ul style="list-style-type: none"> CA for Belgium - > FAGG: via mail to ct.rd@fagg.be CA's other participating countries PI's of participating sites 	Asap, but no later than: <ul style="list-style-type: none"> 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) 7 calendar days (all other reportable events)
	Death	SAE form + narrative	Ethics Committees	Asap
	Annual Progress Report	APR template	<ul style="list-style-type: none"> Ethics Committees CA for Belgium - > FAGG : via CESP portal CA's other participating countries 	Annually

⁴ The SAE report form in excel format can be downloaded from the following web page:
https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

32. QUALITY ASSURANCE AND TRIAL MONITORING

32.1. MONITORING OF THE TRIAL

32.1.1. Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Prof. P. Soubeyran, Coordinating Investigator FRONE and Chairman of the Committee,
- Prof. H. Wildiers, Coordinating Investigator TWOBE and co-chairman of the Committee,
- Principal investigator the Netherlands, geriatric expert (M. Hamaker or a substitute),
- A representative of the sponsor (C. Kenis or a substitute),
- A representative of EUCLID (C. Schwimmer or a substitute)
- The biostatistician of the trial (M. Kret, or a substitute),
- The Methodologist (F. Saillour-Glenisson, or a substitute),
- The coordinating Clinical research manager (C. Duchiron, or a substitute).
- An independent geriatrician (S. Festen, or a substitute)
- An independent oncologist (N. Battisti, or a substitute)
- An independent statistician (F. Canoui-Poitaine, or a substitute)

This committee must ensure the following:

- **Review of the protocol before submission,**
- Implementation and regular follow-up of the study,
- Participant protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated, and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

32.2. QUALITY ASSURANCE

32.2.1. Data collection

Quality of life and various questionnaires will be collected in the same way in both arms through paper questionnaires by study collaborators.

The data will be collected on an electronic case report form (eCRF) and directly input via the Internet. Only the study collaborators appointed by the sponsor and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by an online trial management software on the Internet (Macro v4, Informed Company); it will be transferred and monitored remotely in real time.

The study collaborator appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study collaborator will contact the investigators regarding the study implementation visit.

All of the necessary data will be collected on an electronic case report form (eCRF) provided by the sponsor. The generic names of medication will be given in Dutch.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The investigator or the study collaborator at the authorized centre will validate the case report form whenever data is entered.

32.2.2. Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the KU Leuven/UZ Leuven,
- the quality control of the research site data by a clinical research assistant (CRA) whose role is to:
 - check compliance with the protocol, GCP and current legislation and regulations,
 - check the consent and eligibility of each participant taking part in the trial,
 - check the consistency and coherence of case report form data against the source documents.
 - check that each serious adverse event is reported,
 - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the participants have not participated in a trial for which an exclusion period currently applies.
- The possible audit of study centres,
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form (eCRF) and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each participant (100% level): participant identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, principal response variables. The personal data relating to each participant shall remain confidential. On the electronic case report form (eCRF) or any other form dispatched, the participants will be identified solely by an inclusion number composed of numbers and letters. However, the investigators must keep a list identifying the participants in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant

data required strictly in accordance with this control procedure. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each participant in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

32.2.3. Handling of missing data

The monitoring of data will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

32.2.4. Audits

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit. All the documents relating to this study must be available for such an inspection after prior notification.

CONFIDENTIAL

32.2.5. Data management

The data are entered using an electronic case report form (eCRF) created with Macro 4 (Infermed limited 2010). Data entry is performed by the study collaborator on site using login and password provided by the database administrator. It is carried out at the KU Leuven/UZ Leuven.

Each step of the data management is described in the data management plan (DMP) drafted by the data manager. This document is validated by the coordinating investigator, the statistician, the CRA and the database administrator and is performed according to the internal procedures of the research unit.

The process of data lock/unlock is performed according to our procedure and after validating a check list.

All data will be backed-up daily and kept for 30 days.

33. REGULATORY ASPECTS AND ETHICAL CONSIDERATIONS

33.1. ETHICS COMMITTEE (EC) REVIEW AND REPORTS

Before the start of the trial, this protocol and other related documents (e.g. informed consent forms, investigator's brochure, etc.) will be submitted for review to the Ethics Committee and to the relevant competent authority for trial authorization. The trial shall not commence until such approvals have been obtained and until other relevant essential trial documents, such as duly signed contract agreements, are in place.

It is the responsibility of the coordinating investigator to produce the Annual Progress Report (APR) and submit to the Ethics Committee/competent authority within 30 days of the anniversary date on which favourable opinion to start the trial was given, and annually until the trial is declared ended.

The coordinating investigator shall notify the Ethics Committee/competent authority of the end of the trial. Should the trial be temporarily suspended or, ended prematurely, the coordinating investigator will notify the Ethics Committee/competent authority and include the reasons for suspension/premature termination within 15 days of the decision. The coordinating investigator will submit a final report with the results of the study, including any publications/abstracts, to the Ethics Committee/competent authority within 1 year of trial termination or within 6 months for paediatric trials.

33.2. REGULATORY COMPLIANCE

33.2.1. For Belgium

The trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in Directive 2001/20/EC or EU Regulation 536/2014 or the Regulation (EU) 2017/745 of 5 April 2017 on medical devices, as applicable, and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use or the Belgian law of December 20nd 2020 on medical devices, as applicable, and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

33.2.2. For the Netherlands

The trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in the Good Clinical Practice (decision of 24 November 2006), the Dutch law regarding medical research involving human subjects (WMO), the EU General Data Protection Regulation 2016/679 (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (AVG).

33.3. PROTOCOL / GCP COMPLIANCE

The trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the trial data are credible, reliable and reproducible.

The investigator and trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the coordinating investigator and sponsor. Deviations should also be reported to the Ethics Committee and/or competent authority as part of the EC's continued review of the trial (e.g. through the annual safety report, annual progress report, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the trial participants; or
- the scientific validity of the trial

The investigator is expected to take any immediate action required to protect the safety of any participant included in the trial, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the Ethics Committee and/or competent authority at the trial site should be informed according to local procedures and regulations.

33.4. DATA PROTECTION AND PARTICIPANT CONFIDENTIALITY

The trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian and Dutch laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data and the Dutch law of May 25th 2018 regarding data protection (AVG). Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws. In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR.

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

33.5. INSURANCE POLICY

33.5.1. For Belgian participating sites

Art. 32 of the Belgian Law of December 20nd 2020 on medical devices applies.

Prior to the start of the trial, the sponsor shall enter into an insurance contract in order to adequately cover trial participants from Belgian sites in accordance with art. 32 of the said law.

The KU Leuven/UZ Leuven has obtained an insurance policy (Amlin Insurance SE- Policy number 299.053.700 – Vanbreda Risks & Benefits NV, Plantin en Moretuslei 297, 2140 Antwerpen, Belgium) in case compensation is payable to investigators or participants taking part in the study.

33.5.2. For Dutch participating sites

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Stichting Diaconessenhuis Utrecht has obtained a liability insurance (Policy number 624.100.016 – Onderlinge Waarborgmaatschappij Centramed B.A., Maria Montessorilaan 9, 2719 DB Zoetermeer, the Netherlands) in case compensation is payable to investigators or participants taking part in the study.

33.6. AMENDMENTS

If a substantial amendment to the clinical trial agreement or the documents that supported the original application for the clinical trial authorisation is needed, the sponsor must submit a valid substantial amendment to the Competent Authority (CA) for consideration, and to the Ethics Committee for review and approval. The CA and/or EC will provide a response in accordance with timelines defined by applicable regulations. It is the sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the CA and/or EC.

33.7. INFORMING AND OBTAINING CONSENT FROM PARTICIPANTS

Prior to carrying out medical research on human participants, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the study collaborator and after sufficient time for reflection has been allowed.

The study collaborator in charge of the participant will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The participant can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The participant's written consent will be obtained prior to entry into the study by using the Participant Information Sheet and Informed Consent Form. These forms must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the study collaborator. The original will be given to the participant and the second, archived in the study collaborators folder. Upon request, a copy will be sent to the sponsor in a sealed envelope.

33.8. SPONSOR'S RESPONSIBILITIES

The sponsor of the clinical trial, the KU Leuven/UZ Leuven, will take the initiative for this clinical trial. The KU Leuven/UZ Leuven will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain clinical trial approval for the initial project and any amendments from the EC and inform the FAMHP.
- Give trial-related information to the site directors and investigators,
- Notify the relevant authority of the trial start and end dates,
- Draft the final trial report and sent the summary to FAMHP,
- Send the trial results to the relevant authority, EC and investigators,
- Archive essential trial documents in the sponsor's folder for a minimum period of 25 years after the trial has ended.

33.9. INVESTIGATORS' RESPONSIBILITIES

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee.

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the Ethics Committee having authorized the proposed changes.

It is the responsibility of the principal investigator:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start participant enrollment after authorisation has been obtained from the sponsor,
- to ensure that he/she is available for investigator's meeting and for "monitoring".

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs or eCRFs) for each of the participants enrolled in the trial and to allow the Clinical Research Assistant (CRA) duly authorised by the Sponsor a direct access to source documents so that the latter can validate the data on the CRF or eCRF,
- to date, correct and validate corrections on the case report forms (CRFs or eCRFs) and the Data Query Forms (DQFs),
- to accept regular visits of the CRA and eventually visits of auditors duly authorised by the Sponsor or inspectors of regulatory authorities,
- to inform trial participants of the overall results of the research on first demand.

33.10. AUTHORITY TO EXECUTE THE TRIAL

The investigator shall certify that he/she is authorised to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other agreements that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

33.11. DATA PROCESSING

The data recorded during this research are the subject of a computerised processing on behalf of the sponsor (KU Leuven/UZ Leuven) in accordance with the EU General Data Protection Regulation 2016/679 (GDPR) and relevant Belgian and Dutch national laws implementing the GDPR.

Furthermore, if the biomedical research data is computer processed or managed by computerised systems, each centre:

- shall check and document the fact that the computerised systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation),
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems,
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail),
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access,
- shall update the list of persons authorized to amend the data,
- shall keep appropriate back-up copies of the data,
- shall maintain blind status, where applicable (e.g. during data entry and processing).

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify participants taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these participants to be identified whilst maintaining the confidentiality of the personal data.

The archiving data is performed according to the applicable regulations and under the responsibility of investigator. All data and the participant identification codes will be kept for at least 25 years after the completion or discontinuation of the trial.

34. CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained, and the data and results generated by the trial legally belong to as their obtaining the KU Leuven/UZ Leuven, which can use this data at its own discretion.

According to applicable laws and regulations regarding personal data protection and the processing of personal data, investigators and people who will have to collaborate in the trial shall be bound by professional secrecy with regard to the particular nature of the products studied, trial, trial participants, and results. In particular, all documentation relating to the trial sent to the investigator should be considered confidential information.

Without the consent of the sponsor, the investigator cannot give information about trials to anyone, except the Minister in charge of Public Health, public health medical inspectors, public health pharmacists inspectors, the General Director and inspectors of FAMHP.

The trial cannot be the participant of any written or verbal comments without the sponsor's consent.

35. PUBLICATION AND VALORISATION

35.1. RESEARCH REGISTRATION

The declaration of Helsinki (latest version) and European, Belgian and Dutch regulations require that every research trial involving human participants be registered in a publicly accessible database before recruitment of the first participant.

35.2. SCIENTIFIC COMMUNICATION

All of the information arising from this study shall be considered confidential.

All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities) and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required. In any case, the sponsor will control the first publication.

Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the KU Leuven/UZ Leuven, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial and listing any organizations that have provided financial support.

For the principal publication, either in Dutch, French or English, the authors are:

- the study coordinator
- the investigators will be listed on a pro rata basis according to the number of participants recruited
- persons deeply involved in the trial design and performance
- a representative of the trial statistics unit (in the first 3 positions or two last positions according to degree of involvement in the preparation of publications)

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APPENDIX 1: GERONTE – PROTOCOL FOR PRE- AND POST-IMPLEMENTATION EVALUATION AT CLINICAL TRIAL SITES

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11. BACKGROUND AND RATIONALE

GerOnTe is a 5-year research and innovation project (April 2021 to March 2026) funded by the European Union within the framework of the H2020 Research and Innovation programme, in response to the health societal challenge topic SC1-BHC-24-2020 “Healthcare interventions for the management of the elderly multimorbid patient”. The overall aim of GerOnTe is to improve quality of life - defined as well-being on three levels: global health status, physical functioning, and social functioning- for older multimorbid patients, while reducing overall costs of care. To this end, GerOnTe will co-design, test, and prepare for deployment an innovative cost-effective patient-centred holistic health management system (GerOnTe intervention).

GerOnTe intervention will test the feasibility of integrating the care provided by cancer and other morbidity healthcare professionals into a novel care pathway that is coordinated by an Advanced Practice Nurse (APN) as the case manager. The integration of health professional and patient data will enable shared and improved decision-making and patient-centred personalised care. The intervention will establish; 1. a Health Professional Consortium (HPC), by integrating and coordinating the relevant healthcare professionals; and 2. the processes, the health data (medical, and patient self-reports), and the communication networks and sequence needed to facilitate patient-centred decision-making for patient with cancer and other morbidities. GerOnTe will also aim to design a complimentary application (Holis Patient Application) that will systematise and improve the efficiency of decision-making through the sharing of health and personal data in a secure way.

The GerOnTe intervention will address three important issues experienced in the healthcare system. It will co-create an intervention that is co-designed by stakeholders to work with the **existing systems in place**. GerOnTe will be accompanied by an EU wide implementation guide that provides sufficient detail (of the mechanism of action, the critical and supportive components, and influencing contextual factors) to enable adaption to local setting. GerOnTe will offer a feasible and practical way to bridge the elusive gap between disease-focused model of care and patient-focused models of care (without disintegration of the current models of care that are deeply embedded in current practice and offer many benefits (specialist care themselves). The GerOnTe intervention is an impactful intervention that is expected to offer similar benefits to other population of patient and healthcare providers needing a practical way to build a patient-centred approach into existing systems. The GerOnTe intervention will offer a practical and pivotal solution to the current fragmented system of care, to a more integrated and coordinated care.

The GerOnTe intervention facilitates achieving the triple aim (Berwick, Nolan, and Whittington 2008) to improve quality of life, improve experience of care and reduce costs.

The GerOnTe intervention, therefore, is more than just implementing technology and an Information Communication Technology (ICT) Tool, it is a complete transformational undertaking that impacts an organisation’s people, change management processes, and current and future business models.

Since healthcare system configuration varies from one country to the other and has a strong impact on the delivery of care and on patient health status, an important part of the GerOnTe project is to take into account the context and the organization of healthcare services. This is particularly true for multimorbid patients who often meet several professions, require multiple services, and span different setting and providers. Indeed, the management of older people with multiple conditions challenges usual care delivery, which is frequently structured around pathways of care for single diseases.

A comprehensive and detailed assessment of the clinical trial sites is needed to support successful implementation, scale-up, spread and sustainability, of the GerOnTe intervention and to allow, scientifically robust reporting and dissemination. This will require a significant amount of coordinated, pre-planned but flexible ground work to capture the required scope and depth of accurate data while minimising the burden on local sites and services. This assessment will provide a baseline for a business, economic and implementation evaluation of inputs, context, processes, and outputs.

An essential aspect of the business, economic and implementation evaluation that will be run as part of WP3 and WP5 will be having a good understanding of the baseline processes with a well-developed conceptual model, of how the solution is expected to work (Pawson and Tilley 1997).

12. OBJECTIVES

GENERAL OBJECTIVE

The primary objective of this ancillary study is to inform and support the economic and realistic evaluation, and the GerOnTe Business Plan to support wider EU dissemination of the GerOnTe model. A critical and time-sensitive aspect of this ancillary study is the identification and collection of all relevant data to enable meaningful analysis and documentation to support robust empirical reporting and analysis.

SPECIFIC OBJECTIVES

The specific objectives of this study are to:

4. identify, describe, analyse, and map the common and distinctive elements and gaps of the current care pathways for older multimorbid patients with cancer as a dominant morbidity within each clinical sites involved, including the preparation of process maps showing the initial state of the care pathway (Kononwech et al 2020).
5. document and analyse the process of implementation of the intervention in the trial sites beyond the specific trial outcomes to enable analysis of the mechanism of action of the intervention, the contextual factors and barriers and facilitators to implementation and application of the GerOnTe intervention (to develop a comprehensive implementation guide that will inform implementation across diverse settings).
6. evaluate the impact of the GerOnTe intervention on the evolution of practices and organizations at hospitals and build recommendations for its deployment in other contexts.

13. ELIGIBILITY CRITERIA

Each clinical site participating in the trial will be involved in the ancillary study.

In each clinical site, the principal investigator (PI) will identify and recruit relevant staff members (e.g., physicians, nurses, clinical and financial managers, IT and administrative staff), and a small selection of patients/family members/carers following a stakeholder analysis approach (Brugha and Varvasovszky, 2000). Therefore all the relevant stakeholders who can inform the understanding of the behaviours, intentions, agendas, interests, interrelations, and the influence or resources that will impact the intervention and its implementation will be identified, recruited, and involved. The PI will provide the research team with the comprehensive list of relevant stakeholders to be interviewed for the purposes of the Ancillary study.

This data will be used to inform and support successfully:

4. Evaluation of the current and post-GerOnTe implemented care pathways in each clinical trial site;
5. Implementation of the intervention at each clinical trial site;

6. Deliverables on the business, economic, and implementation evaluations.

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14. SAMPLE SIZE AND METHOD

A baseline assessment will involve a number of qualitative methods (e.g., questionnaires, semi-structured interviews and focus groups) with the relevant stakeholders. The choice between questionnaires, individual interviews and focus groups (FG), and between end-user specific (such as patient only FG) and mixed FG (such as clinicians and patients) will be determined by the FG / interview aim, stage of the assessment (pre, during or post trial), and the practical factors such as participants' availability and preferences. However, the ancillary study will aim to organise and support mixing and collaboration between stakeholders in line with the GerOnTe's broader end-user focused and collaborative approach.

The relevant stakeholders to involve will be selected with the support of the principal investigator in each clinical site. The number of participants included will depend upon the number required to inform all important elements of the phenomenon being studied (when data saturation is achieved). We expect that approximately 3-5 staff members and 5-10 patients and/or family members/carers (from both the intervention and the control arm) will be involved in each site over the entire duration of the project resulting in a total of approximately 20-30 staff members and 40-60 patients across all sites). The sample size will be evidenced as sufficient when additional interviews or focus groups do not result in emergence of new concepts. This inductive approach allows us to document the emergence of new themes and also to identify perspectives that may otherwise be overlooked (Sargeant 2012).

15. OUTCOMES

The outcome of the study will be:

3. A map of the current care pathways, people, formal and informal processes, and technology, and a descriptive analysis of the current care pathway for older multimorbid patients with cancer as dominant morbidity, in each clinical site. This will represent the pre-GerOnTe context for each site.
4. A descriptive analysis that identifies the (GerOnTe) mechanism of action, and the contextual factors that can act as barriers or facilitators to the intervention or its implementation, with an accompanying guidance document that supports widespread implementation of GerOnTe.

16. ANCILLARY PROCEDURES

Data will be collected, using both qualitative and quantitative approaches, including interviews, focus groups, questionnaires, direct observation, and document review.

The relevant document to inform the implementation, economic and business case reports will be identified in collaboration with the trail site PI or their designated person. Key documents will include the organisation's formal policies and reports related to clinical and business practice, processes, standards, and outcomes, minutes of relevant meetings, and documentation from multidisciplinary team (MDT)/health professional consortium (HPC) meetings. Neither patient nor clinical details will be sought, accessed, nor recorded, as this is purely a review of MDT processes.

The intents are:

3. to document the care pathways and the consumption patterns of multimorbid older patients with cancer as dominant morbidity before and after the introduction of GerOnTe. The care pathways will be analysed according to the various phases of the care process: noticing the symptoms and first detection, assessment and diagnosis, treatment and care service definition, and service delivery and follow-up.

4. to collect data on:

- the contexts and implementation processes at each trial site,
- Patients, physician and health professional experience with Holis Patient App and with GerOnTe,
- Individual and collective barriers and facilitators to GerOnTe intervention implementation and usage,
- The impact of the GerOnTe intervention on the evolution of practices and organizations at hospital level, for health professionals.

This work will be done in the relevant local languages, with fieldwork conducted by the research team.

In each clinical site participating in the trial, we will follow the undermentioned flow (figure 5) and procedures (for the Principal investigator and the involved researchers).

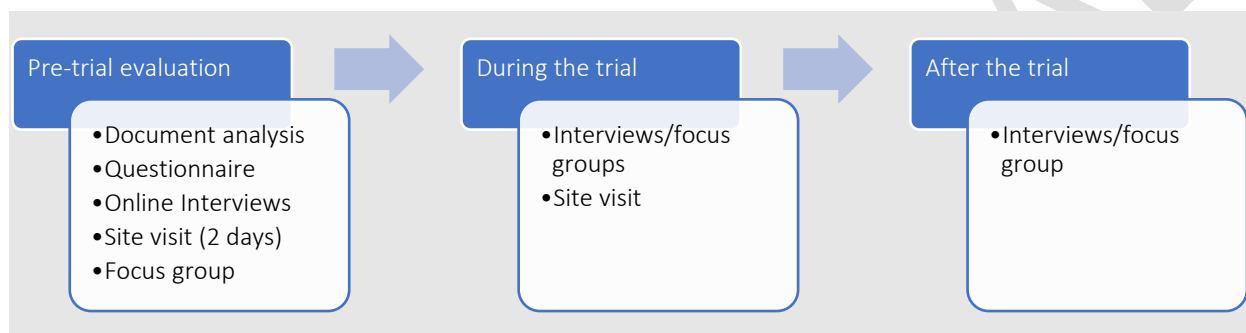


Figure 5

Procedure for the Principal investigator

For each site, before the trial starts the PI:

- Will make sure to identify and share with the research team relevant document about the clinical site (e.g., organisation policies, reports, etc.),
- Will make sure that the identified stakeholders complete a questionnaire that will be sent to them,
- Will make available the identified stakeholders for Zoom interviews (or other similar teleconference technologies),
- Will support the scheduling and organization of on-site visits of the research team.

For each site, during the trial, the PI:

- Will make sure that the identified stakeholders participate in the follow-up interviews and focus groups,
- Will support the scheduling and organization of on-site visits of the research team.

Procedure for the researcher

BEFORE THE INTERVIEW

- Explain the objective of the interview to the relevant stakeholders (e.g., physicians, nurse, clinical and financial managers, IT and administrative staff), identified by the site principal investigator,
- Obtain agreement to an interview.

DURING THE INTERVIEW

- Collect informed written consent,
- Carry out an interview, collecting data as described below, and arranging for it to be recorded, if the participant(s) agree, and transcribed for further analysis (in line with GDPR and local ethics requirements),
- Identify from the interviews key documents, arrange access to these, and review them.

AFTER THE INTERVIEW

- Summarize the collected information and analyse them,
- Prepare a report on the initial state and final state for each centre in a manner and level of detail that enables achievement of the outcomes set out above,
- Share the relevant analysis with Partners involved in the trial to enable implementation of the intervention at individual trial sites in a way that considers the differences (that may impact the intervention success),
- use the information collected to inform the business, economic and implementation evaluation, and guidance documentation.

6.1 Questionnaires

Introduction: The aim of the questionnaire is to collect data on the organizational model of the site participating in the project and in particular the delivery and service model before conducting an interview. The focus is on older people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

6.1.1 For Clinical site Principal investigator

The questionnaire will cover these domains:

- Volumes of activities and patient characteristics (e.g., how many patients are treated by the centre, age group, needs) (*Patient volume planning and control*),
- Long-term policy of the institution (*strategic planning*),
- Institutional engagement, experience, or policy document supporting change management,
- Operational strategy, in terms of available professionals, equipment and space (*resource planning and control*),
- Multidisciplinary models (e.g. MDT),
- Institutional funding model (public/ private/ mixed), and service type and use by proportion of public/ private patients (if mixed),
- Relevant recent or current service or innovation changes or improvement taking place,
- Patient engagement and feedback procedures,
- Staff recruiting, training, development, and retention and service development practices,
- Professional representation and decision-making around service delivery,
- Patient representation and decision-making around service delivery.

6.1.2 For Clinical trial site staff (clinicians, and clinical, business, technology managerial staff):

The questionnaire will cover these domains:

- Employment experience related to GerOnTe (complex) patient population,
- Experience with integrated care at existing or previous work,
- Experience, views, and awareness of their organisation's policies and supports around change management,
- Previous experience and views around implementing complex or technology in their clinical setting,
- Experience and views around potential challenges, competitors and facilitators to implementing complex technology change in their setting.

6.2 Semi-structured interview

Introduction: The aim of the interviews is to describe the organizational model of the site participating in the project and in particular the delivery and service model. We're especially interested in people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

6.2.1 For Clinical site Principal investigator (for all 8 participating sites)

BEFORE IMPLEMENTATION OF GERONTE INTERVENTION

- Can you explain the long-term policy of the institution (*strategic planning*)?
- Can you explain the organizational model of the site?
 - Describe core and peripheral contents of the service offered by the centre.
 - Patient access points, process standardization, interaction methods with patients and families
 - Services dedicated to taking charge of the patient (e.g., physical location, organizational dependence, dedicated clinics, specialization)
- Can you describe how older people with cancer and other complex health needs are cared for right now – is there a formal care pathway, or how is it done? (*Patient planning and protocol*)
 - Description of the care pathway in the different phases: sending, diagnosis, treatment and follow up
 - Who is involved? What do they do? When? Where? Why?
- How do you interact with other professionals / specialties and nodes of the network (e.g., GP, other professionals, facilities, other units)?
- Do you have regular team meetings – multi-disciplinary team meetings? For which patients? How do these meetings work?
- What difficulties do you currently face in the management of older multimorbid patients?
- What work, or informal practices do you do, or try to do, to fix problems or delays in the system? How do you typically access and share information about your patients?

AFTER INTRODUCTION OF GERONTE INTERVENTION

- Speaking of the GerOnTe pathway, what did you have to do to make it happen in your service?
- What did other people have to do?
- From your point of view, is it working well in your service?
- What would you like to change to improve it or make it work better?
- What helped you bringing in this new pathway?
- What got in the way of bringing in the new pathway?
- Specifically, how is the new technology working for you and your colleagues?
- Does this technology impact (in a good or bad way) on any other technology you use or work you do?
- How do you think the technology is going for other colleagues, and for patients and their families?
- Overall, do you feel GerOnTe has affected your work – has it been a good experience or a bad experience? What were the benefits, and the costs, of GerOnTe from your perspective?
- Do you think GerOnTe will continue to be used on your service when the study is over?

6.2.1 FOR STAFF MEMBERS (HPC)

BEFORE IMPLEMENTATION OF GERONTE INTERVENTION

Introduction: We'd like to talk a bit with you about how care is delivered to older people with cancer in your service. We're especially interested in people who have cancer, but also have some other health issues. These might be single conditions like diabetes or COPD, or more complex conditions like frailty, or both.

- Can you describe how older people with cancer and other complex health needs are cared for right now – is there a formal care pathway, or how is it done?
 - Description of the care pathway in the different phases: sending, diagnosis, treatment and follow up
 - Who is involved? What do they do? When? Where? Why?
 - Do patients need to initiate or follow up on much of the care?
 - Do you think certain groups are disadvantaged and how?
- What makes care work well? What makes care doesn't work well?
- What gets in the way of delivering the care you would like to give?
- What would you like to see that you haven't yet have?
- Do you have regular team meetings – multi-disciplinary team meetings? How do these meetings work?
- How do you typically access and share information about your patients?
- What would improve this communication process?
- How do you interact with other professionals and nodes of the network (e.g., GP, other professionals, facilities, other units)?

INTRODUCTION OF GERONTE

- How are you involved in bringing in this new care pathway?
- What do you think it should achieve to be useful?
- Do you see challenges to bringing in this care pathway? And what do you expect it will achieve?
(plus follow on of why do you think it will achieve this [lesser goal])
- How was/will it be brought into use in your service?

AFTER INTRODUCTION OF GERONTE INTERVENTION

- Speaking of the GerOnTe intervention, what did you have to do to make it happen in your service?
- What support/ information/ teaching did you get on GerOnTe, your role in GerOnTe, and how GerOnTe should be implemented?
- What did other people have to do?
- From your point of view, is it working well in your service?
- What helped you bringing in this new pathway?
- What got in the way of bringing in the new pathway?
- Specifically, how is the new technology going for you and your colleagues?
- How do you think the technology is going for other colleagues, and for patients and their families?
- Overall, do you feel GerOnTe has affected your work – has it been a good experience or a bad experience? What were the benefits, and the costs, of GerOnTe from your perspective?
- Do you think GerOnTe will continue to be used on your service when the study is over?
- If GerOnTe was staying, what would you change about it?

6.2.2 PATIENTS, FAMILY, AND CAREGIVERS

INTRODUCTION:

We're looking at how care is given to older people like you (your relative) with cancer in this hospital. We're trying to understand how care is done and get some understanding of how this affects you. We're especially interested in how information about you, and about how you are doing, is shared with you and with your doctors, nurses, and other health care professionals.

- How are you finding the care you get here all-in-all?
- Do the people you meet know what you expect them to know about, you, about your treatment, and about your progress?
- Do you find yourself having to tell the same things to different people, or do you feel that they are sharing what you've told them about you?
- Do you know, more or less, what's happening with your treatment?

- Who would you go to if there was a problem, you thought might be related to your treatment?
- Who would you go to for a problem, maybe with a condition you already have, that isn't related to your treatment?
- What has helped you most in your care journey?

For patients using the GerOnTe Patient App:

- What is your general opinion about using the app?
- How is it useful to you?
- What else would be helpful to you?
- What encourages you to use it?
- What puts you off using it?

FOR PATIENTS NOT USING THE GERONTE PATIENT APP

- How do you see yourself using an app?
- Would you find it useful to you?
- What would encourage you to use it?
- What would put you off using it?

17. RECRUITMENT AND CONSENT

All participants involved in the study will sign an interview informed consent form (hereafter referred to as 'Form'). The form will collect the following information:

3. Confidential Personal Data (as defined by the GDPR, 2018) such as – Name of interviewee, age, gender, grade, and specific role of participant, and date of interview. This will be managed in line with GDPR (2018), local ethical requirements, and participants' wishes.
4. Open information:
 - Site
 - General role (e.g., patient, oncologist, nurse, ...)
 - Description of interview setting – one-on-one, team interview (focus group)

Moreover, the Form will include a brief description of the project, the terms, and conditions of being a participant, a signature from the researcher and from the participant.

18. DATA MANAGEMENT

The purpose of data collection will be to gather the necessary information:

5. relating to the context of each site,
6. relating to the implementation of GerOnTe intervention in each clinical site,
7. to develop a robust economic evaluation that support the broader and complex value of the GerOnTe intervention,

8. To develop an empirically based Business Plan to support widespread dissemination of the GerOnTe intervention.

Data will be managed and disseminated in line with GDPR (2018), the GERONTE Data Management Plan and section §4.6.1 and 4.6.2 of the GerOnTe consortium agreement signed by all beneficiary partners.

The Data recorded during this research will be collected, stored and analysed in accordance with the Data Protection Laws. Each Party involved will provide adequate measures to ensure Data protection and, confidentiality regarding local, national, and international rules on data protection. The data collected will be stored in selectively accessible folder, anonymized and functionally separated. Each step of the data management is described in the data management plan (DMP) drafted by the data manager.

19. STATISTICAL AND DATA ANALYSIS

Given the complexity of the study, the analysis will adopt both a deductive and inductive approach.

A mixed inductive-deductive approach will be used to map the patient journey within each clinical site before the implementation using data collected from interview and document review. The researcher will collect data relevant to analyse the context (Phase 1 – Gather data), and once a substantial amount of data have been collected, we will look for patterns in the data (Phase 2 – analysis), working to develop a theory that could explain those patterns (Phase 3 – Develop Theory).

The implementation evaluation will use a more deductive approach and will use evidenced-based Implementation Science theory and framework to guide the data collection, analysis, synthesis, and development of an EU wide Implementation Guide (D5.4) and GerOnTe [Guide] to Implementation and Challenges D5.2. The implementation evaluation will also be sensitive to, and will be shaped and informed, inductively to ensure an implementation evaluation and guide that captures the broad and complex scope of the GerOnTe intervention. Interview, questionnaire, document review and observation (of non patient-care) processes will be analysed in line with the relevant qualitative and quantitative relevant evidenced-based techniques.

Development of the Business Case will involve close collaboration with relevant Partners to support and guide identification of the type and depth of data to be collected to support the development of a Business Case that representative of GerOnTe's scope and aim. The relevant data will be identified, collected, and analysed. A key aim is to identify and ensure the robustness of sources and collection methods in order to facilitate development of a Business Case that will provide solid and effectual argument of the value of the GerOnTe intervention.

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APPENDIX 2: EORTC QLQ-C30

DUTCH

**EORTC QLQ-C30 (versie 3)**

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is? Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw initialen invullen:

--	--	--	--	--

Uw geboortedatum (Dag, Maand, Jaar):

--	--	--	--	--	--	--	--	--	--

De datum van vandaag (Dag, Maand, Jaar):

31

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	Helemaal niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2. Heeft u moeite met het maken van een <u>lange</u> wandeling?	1	2	3	4
3. Heeft u moeite met het maken van een <u>korte</u> wandeling buitenshuis?	1	2	3	4
4. Moet u overdag in bed of op een stoel blijven?	1	2	3	4
5. Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:

	Helemaal niet	Een beetje	Nogal	Heel erg
6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7. Was u beperkt bij het uitoefenen van uw hobby's of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8. Was u kortademig?	1	2	3	4
9. Heeft u pijn gehad?	1	2	3	4
10. Had u behoefte om te rusten?	1	2	3	4
11. Heeft u moeite met slapen gehad?	1	2	3	4
12. Heeft u zich slap gevoeld?	1	2	3	4
13. Heeft u gebrek aan eetlust gehad?	1	2	3	4
14. Heeft u zich misselijk gevoeld?	1	2	3	4
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (was u verstopt?)	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan.

DUTCH

Gedurende de afgelopen week:

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd bij uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het zich herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw <u>familieleven</u> in de weg staan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd bij uw <u>sociale</u> bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is?

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

APPENDIX 3: EORTC QLQ-ELD14

DUTCH

**EORTC QLQ-ELD14**

Soms zeggen patiënten dat ze volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze symptomen of problemen gedurende de afgelopen week heeft ervaren? Wilt u uw antwoord geven door het cijfer te omcirkelen dat het meest op u van toepassing is.

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
31. Heeft u moeilijkheden gehad met treden of trappen?	1	2	3	4
32. Heeft u problemen gehad met uw gewrichten (b.v. stijfheid, pijn)?	1	2	3	4
33. Voelde u zich onvast op uw benen staan?	1	2	3	4
34. Had u hulp nodig bij huishoudelijke klusjes zoals schoonmaken of boodschappen doen?	1	2	3	4
35. Heeft u zich in staat gevoeld om met uw familie over uw ziekte te praten?	1	2	3	4
36. Heeft u zich zorgen gemaakt over hoe uw familie met uw ziekte en behandeling omgaat?	1	2	3	4
37. Heeft u zich zorgen gemaakt over de toekomst van mensen die belangrijk zijn voor u?	1	2	3	4
38. Maakte u zich zorgen over uw gezondheid in de toekomst?	1	2	3	4
39. Voelde u zich onzeker over de toekomst?	1	2	3	4
40. Heeft u zich zorgen gemaakt over wat er zou kunnen gebeuren naar het einde van uw leven toe?	1	2	3	4
41. Heeft u in de afgelopen week een positieve kijk gehad op het leven?	1	2	3	4
42. Heeft u zich gemotiveerd gevoeld om uw normale hobby's en activiteiten voort te zetten?	1	2	3	4
43. In welke mate is uw ziekte een belasting voor u geweest?	1	2	3	4
44. In welke mate is uw behandeling een belasting voor u geweest?	1	2	3	4

APPENDIX 4: KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING (KATZ ADL)

Criterion	Score	Onafhankelijk (1 punt)	Afhankelijk (0 punten)
WASSEN	Wast zichzelf volledig onafhankelijk of wordt slechts geholpen voor één onderdeel (bv. het wassen van de rug of een gehandicapt lichaamsdeel)	Heeft hulp nodig bij het wassen van meer dan één lichaamsdeel; heeft hulp nodig om in en/of uit bad te komen of wacht zichzelf helemaal niet
KLEDEN	Neemt zelf de kledingstukken uit de kast of lade, kleedt zichzelf aan en kan losse kledingstukken zonder problemen aandoen. Het vastbinden van de schoenveters wordt niet beoordeeld	Heeft gedeeltelijke of volledige hulp nodig bij het kleden
WC-BEZOEK	Kan zich zonder hulp verplaatsen naar of van het toilet, zich neerzetten en rechtekomen van het toilet en zichzelf reinigen. Gebruik van mechanische hulpmiddelen is toegelaten	Heeft gedeeltelijke of volledige hulp nodig voor de verplaatsing naar het toilet, het reinigen of gebruikt een bedpan
VERPLAATSEN	Kan zich volledig zelfstandig in en uit een bed of een fauteuil verplaatsen. Gebruik van mechanische hulpmiddelen is toegelaten	Heeft hulp nodig om in en uit een bed of fauteuil te komen; doet geen zelfstandige verplaatsingen
CONTINENTIE	Is continent voor urine en faeces	Is volledig of gedeeltelijk incontinent voor urine of faeces
VOEDEN	Neemt het voedsel zelf van het bord en eet zelfstandig. Voorbereidende handelingen worden niet geëvalueerd	Heeft gedeeltelijke of volledige hulp nodig bij de voeding of heeft parenterale voeding nodig
Totaalscore (0-6)		

APPENDIX 5: CLINICAL FRAILTY SCALE

Score	Categorie fitheid	Toelichting
	1. Erg fit	Personen die krachtig, actief, energiek en gemotiveerd zijn. Deze ouderen doen regelmatig aan sport. Ze behoren tot de fitste voor hun leeftijd.
	2. Fit	Personen die geen actieve ziektesymptomen vertonen, maar minder fit zijn dan in categorie 1. Ze doen vaak aan sport of zijn occasioneel fysiek zeer actief, bijvoorbeeld seizoensgebonden.
	3. Gezond	Personen bij wie medische problemen goed onder controle zijn, maar die niet op regelmatige basis fysiek actief zijn op hun dagelijkse verplaatsingen na.
	4. Pre-frail	Personen die niet afhankelijk zijn van anderen voor dagelijkse activiteiten; maar bij wie symptomen vaak hun activiteiten beperken. Een vaak gehoorde klacht is langzamer zijn en/of vermoeidheid doorheen de dag.
	5. Mild frail	Deze personen zijn zichtbaar trager in hun activiteiten en hebben hulp nodig in de complexere iADL-taken (regelen van de financiën, transport, zware huishoudelijke taken, medicatie- beheer). (ADL onafhankelijk). De milde frailty zal geleidelijk aan volgende activiteiten belemmeren: alleen boodschappen doen en zich alleen buitenshuis verplaatsen, maaltijd bereiden en het uitvoeren van huishoudelijke taken.
	6. Matig frail	Deze personen hebben hulp nodig bij alle activiteiten buitenshuis en met huishoudelijke taken. Binnenshuis, hebben ze vaak problemen met trappen, en hebben ze hulp nodig bij het zich wassen, en hebben ze minimale begeleiding nodig bij het zich kleden (toezicht, aanwijzingen geven). (ADL gedeeltelijk afhankelijk).
	7. Ernstig frail	Volledig afhankelijk voor persoonlijke zorg ongeacht de oorzaak (fysiek of cognitief). Ondanks hun zorgnood lijken ze stabiel en lijkt er geen verhoogd risico op overlijden (binnen de 6 maanden). (ADL volledig afhankelijk).
	8. Zeer ernstig frail	Volledig afhankelijk en naderen het einde van het leven. Deze personen kunnen vaak niet herstellen van een mineure ziekte zoals een verkoudheid.
	9. Terminaal ziek	Deze categorie is van toepassing op personen die het einde van hun leven naderen met een levensverwachting ≤ 6 maanden, die anders niet duidelijk frail zijn.

APPENDIX 6: ECOG-PS

ECOG Performance Status	Graad
Normale activiteit zonder beperkingen.	0
Beperkt in activiteiten die een fysieke inspanning vereisen. In staat om te wandelen en licht werk uit te voeren.	1
Mobiel en volledig in staat tot zelfzorg. Niet in staat om enig werk te doen gedurende meer dan de helft van de dag.	2
In staat tot beperkte zelfzorg. Meer dan de helft van de dag gekluisterd aan bed of stoel.	3
Volledig invalide. Geen enkele mogelijkheid tot zelfzorg. Gekluisterd aan bed of stoel.	4
Dood	5
Score

APPENDIX 7: HADS

	Meestal	Vaak	Af en toe, soms	Helemaal niet
1. Ik voel me de laatste tijd gespannen.	3	2	1	0
2. Ik geniet nog steeds van de dingen waar ik vroeger van genoot.	3	2	1	0
3. Ik krijg de laatste tijd het angstige gevoel alsof er elk moment iets vreselijks zal gebeuren.	3	2	1	0
4. Ik kan lachen en de dingen van de vrolijke kant zien.	3	2	1	0
5. Ik maak me de laatste tijd ongerust.	3	2	1	0
6. Ik voel me de laatste tijd opgewekt.	3	2	1	0
7. Ik kan de laatste tijd rustig zitten en me ontspannen.	3	2	1	0
8. Ik voel me de laatste tijd alsof alles moeizamer gaat.	3	2	1	0
9. Ik krijg de laatste tijd een soort benauwd, gespannen gevoel in mijn maag.	3	2	1	0
10. Ik heb de laatste tijd geen interesse meer in mijn uiterlijk.	3	2	1	0
11. Ik voel me de laatste tijd rusteloos.	3	2	1	0
12. Ik verheug me van tevoren al op dingen.	3	2	1	0
13. Ik krijg de laatste tijd plotseling gevoelens van angst of paniek.	3	2	1	0
14. Ik kan van een goed boek genieten of een radio- of televisieprogramma.	3	2	1	0
Totaalscore HADS (0-42)			
Totaalscore oneven vragen HADS (0-21) – ANGST			
Totaalscore even vragen HADS (0-21) – DEPRESSIE			

APPENDIX 8: EQ-5D-5L

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

- | | |
|---------------------------------------|--------------------------|
| Ik heb geen problemen met lopen | <input type="checkbox"/> |
| Ik heb een beetje problemen met lopen | <input type="checkbox"/> |
| Ik heb matige problemen met lopen | <input type="checkbox"/> |
| Ik heb ernstige problemen met lopen | <input type="checkbox"/> |
| Ik ben niet in staat om te lopen | <input type="checkbox"/> |

ZELFZORG

- | | |
|---|--------------------------|
| Ik heb geen problemen met mijzelf wassen of aankleden | <input type="checkbox"/> |
| Ik heb een beetje problemen met mijzelf wassen of aankleden | <input type="checkbox"/> |
| Ik heb matige problemen met mijzelf wassen of aankleden | <input type="checkbox"/> |
| Ik heb ernstige problemen met mijzelf wassen of aankleden | <input type="checkbox"/> |
| Ik ben niet in staat mijzelf te wassen of aan te kleden | <input type="checkbox"/> |

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

- | | |
|---|--------------------------|
| Ik heb geen problemen met mijn dagelijkse activiteiten | <input type="checkbox"/> |
| Ik heb een beetje problemen met mijn dagelijkse activiteiten | <input type="checkbox"/> |
| Ik heb matige problemen met mijn dagelijkse activiteiten | <input type="checkbox"/> |
| Ik heb ernstige problemen met mijn dagelijkse activiteiten | <input type="checkbox"/> |
| Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren | <input type="checkbox"/> |

PIJN / ONGEMAK

- | | |
|-----------------------------------|--------------------------|
| Ik heb geen pijn of ongemak | <input type="checkbox"/> |
| Ik heb een beetje pijn of ongemak | <input type="checkbox"/> |
| Ik heb matige pijn of ongemak | <input type="checkbox"/> |
| Ik heb ernstige pijn of ongemak | <input type="checkbox"/> |
| Ik heb extreme pijn of ongemak | <input type="checkbox"/> |

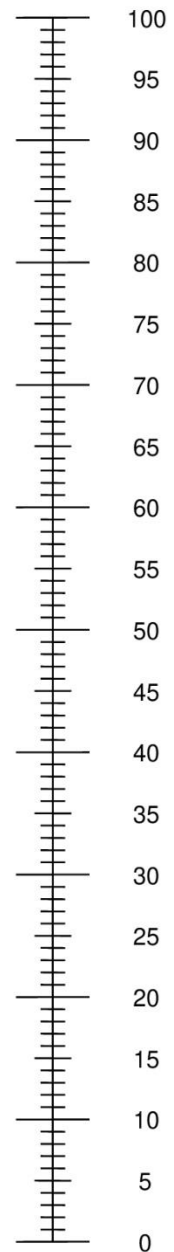
ANGST / SOMBERHEID

- | | |
|-------------------------------------|--------------------------|
| Ik ben niet angstig of somber | <input type="checkbox"/> |
| Ik ben een beetje angstig of somber | <input type="checkbox"/> |
| Ik ben matig angstig of somber | <input type="checkbox"/> |
| Ik ben erg angstig of somber | <input type="checkbox"/> |
| Ik ben extreem angstig of somber | <input type="checkbox"/> |

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen.
0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG =

De beste gezondheid
die u zich kunt
voorstellen



De slechtste
gezondheid die u
zich kunt voorstellen

APPENDIX 9: ZARIT BURDEN INTERVIEW

	Bijna altijd	Redelijk vaak	Soms	Zelden	Nooit
1. Vindt u dat uw familielid meer hulp vraagt dan hij/zij nodig heeft?	4	3	2	1	0
2. Vindt u dat u niet genoeg tijd voor uzelf hebt vanwege de tijd die u doorbrengt met uw familielid?	4	3	2	1	0
3. Voelt u zich gespannen door de combinatie van de zorg voor uw familielid en de andere verantwoordelijkheden die u probeert na te komen voor uw gezin of uw werk?	4	3	2	1	0
4. Voelt u zich opgelaten door het gedrag van uw familielid?	4	3	2	1	0
5. Bent u boos op uw familielid als u met hem/haar samen bent?	4	3	2	1	0
6. Vindt u dat uw familielid momenteel een negatieve invloed heeft op uw relatie met andere familieleden of vrienden?	4	3	2	1	0
7. Bent u bang voor wat de toekomst brengen zal voor uw familielid?	4	3	2	1	0
8. Vindt u dat uw familielid afhankelijk is van u?	4	3	2	1	0
9. Voelt u zich gespannen als u samen met uw familielid bent?	4	3	2	1	0
10. Vindt u dat uw gezondheid lijdt onder de zorg voor uw familielid?	4	3	2	1	0
11. Vindt u dat u vanwege uw familielid minder privacy hebt dan u zou willen?	4	3	2	1	0
12. Vindt u dat uw sociale leven lijdt onder uw zorg voor uw familielid?	4	3	2	1	0
13. Voelt u zich vanwege uw familielid, ongemakkelijk bij het idee om vrienden te ontvangen?	4	3	2	1	0
14. Vindt u dat uw familielid van u lijkt te verwachten dat u voor hem/haar zorgt, alsof u de enige bent op wie hij/zij kan rekenen?	4	3	2	1	0
15. Vindt u dat u, naast uw andere uitgaven, niet genoeg geld hebt om voor uw familielid te zorgen?	4	3	2	1	0
16. Hebt u het gevoel dat u niet veel langer meer voor uw familielid zult kunnen zorgen?	4	3	2	1	0
17. Vindt u dat u de controle over uw eigen leven verloren hebt sinds de ziekte van uw familielid?	4	3	2	1	0

18. Zou u de zorg voor uw familielid eigenlijk het liefst willen overlaten aan iemand anders?	4	3	2	1	0
19. Voelt u zich onzeker over wat u met uw familielid aan moet?	4	3	2	1	0
20. Vindt u dat u meer zou moeten doen voor uw familielid?	4	3	2	1	0
21. Vindt u dat u beter voor uw familielid zou kunnen zorgen?	4	3	2	1	0
22. Hoe belast voelt u zich over het algemeen bij het zorgen voor uw familielid?	4	3	2	1	0
Totaalscore ZBI (0-88)				

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APPENDIX 10: P3CEQ

CONFIDENTIAL

START VAN HET INTERVIEW

Deze vragenlijst gaat over uw ervaringen met en uw inzicht in de zorg en ondersteuning die u heeft ontvangen van uw zorgverleners in de gemeente Medemblik gedurende de afgelopen [tijd].

De komende vragen gaan over 'zorg' die u ontvangen heeft. Met 'zorg' bedoelen wij alle zorg en ondersteuning die u heeft ontvangen op het gebied van uw gezondheid en welzijn.

Van wie heeft u gedurende de afgelopen [tijd] zorg ontvangen? Kruis aan wat van toepassing is, er zijn meerdere opties tegelijkertijd mogelijk.

Huisarts (incl. praktijkondersteuner)	<input type="checkbox"/>	(Wijk)verpleegkundige	<input type="checkbox"/>
Welzijnswerk	<input type="checkbox"/>	Geestelijke gezondheidszorg	<input type="checkbox"/>
Ziekenhuis (opname)	<input type="checkbox"/>	Ziekenhuis (poliklinisch)	<input type="checkbox"/>
Een therapeut (bijv. fysiotherapeut)	<input type="checkbox"/>	WMO ondersteuning vanuit de gemeente	<input type="checkbox"/>
Vrijwilligers (bijv. De Zonnebloem)	<input type="checkbox"/>	Anders, zoals	<input type="checkbox"/>

Indien u zorg heeft ontvangen van meerdere zorgprofessionals en/of informele hulpverleners, baseert u uw antwoord op de onderstaande vragen op uw algehele ervaring met deze zorg.

Gebruik a.u.b. bij iedere vraag de ruimte voor toelichting om relevante of opvallende voorbeelden te noteren.

- 1. Bespreekt u met uw zorgverlener(s) wat VOOR U het meest belangrijk is om te kunnen werken aan uw gezondheid en welzijn?**

Nooit	<input type="checkbox"/>	Toelichting
Soms	<input type="checkbox"/>	
Meestal	<input type="checkbox"/>	
Altijd	<input type="checkbox"/>	
Niet van toepassing	<input type="checkbox"/>	

2. Werd u voldoende betrokken bij beslissingen over uw zorg?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

3. Was er aandacht voor u als persoon en niet alleen voor uw ziekte of aandoening?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

4. Is het wel een voorgekomen dat u uw verhaal meerdere keren aan uw zorgverlener(s) moest vertellen?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Niet van toepassing		

5. Vindt u dat de zorg die u van uw verschillende zorgverleners ontvangt goed op elkaar aansluit?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Er is maar één zorgverlener (bijv. de huisarts) van wie ik zorg ontvang		
Niet van toepassing		

6. Heeft u een aanspreekpunt vanuit de zorg(organisatie), die verantwoordelijk is voor het regelen van de zorg en ondersteuning die u ontvangt?

Ja		Toelichting:
Nee		
Weet ik niet		

7a. Heeft u een zorgplan waarin uw wensen op het gebied van uw gezondheid en welzijn zijn opgenomen?

Ja <i>Ga door naar de vragen 8b, 8c en 8d</i>		Toelichting:
Nee <i>Ga door naar vraag 9</i>		
Weet ik niet <i>Ga door naar vraag 9</i>		

7b. Heeft u een kopie van uw zorgplan thuis?

Ja		Toelichting:
Nee		
Weet ik niet		

7c. In hoeverre is het zorgplan bruikbaar VOOR U om aan uw gezondheid en welzijn te kunnen werken?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Weet ik niet		

7d. Denkt u dat alle zorgverleners, die betrokken zijn bij uw zorg, hetzelfde zorgplan gebruiken?

Nooit		Toelichting:
Soms		
Meestal		
Altijd		
Weet ik niet		

8. Heeft u voldoende ondersteuning gekregen van uw zorgverlener(s) om aan uw gezondheid en welzijn te kunnen werken?

Ik heb geen ondersteuning nodig		Toelichting:
Ik heb geen ondersteuning gekregen		
Ik heb soms voldoende ondersteuning gekregen		
Ik heb vaak voldoende ondersteuning gekregen		
Ik heb altijd genoeg ondersteuning gekregen		
Niet van toepassing		

9. Kreeg u voldoende bruikbare informatie op het moment dat u dit nodig had, om te kunnen werken aan uw gezondheid en welzijn?

Ik ontvang geen informatie		Toelichting:
Ik ontvang soms voldoende informatie		
Ik ontvang vaak voldoende informatie		
Ik ontvang altijd voldoende informatie		
Ik ontvang te veel informatie		
Niet van toepassing		

10. Hoe zeker bent u ervan dat u in staat bent om zelf te werken aan uw gezondheid en welzijn?

Totaal niet zeker		Toelichting:
Niet zo zeker		
Redelijk zeker		
Erg zeker		
Niet van toepassing		

Optionele vraag, indien uw partner, kinderen of andere mantelzorgers bij uw afspraken met zorgverleners aanwezig zijn:

11. Werden uw partner, kinderen of andere mantelzorgers door uw zorgverlener(s) voldoende betrokken bij beslissingen over uw zorg?

Nooit		Toelichting:
Soms		

Meestal		
Altijd		
Ik wilde niet dat mijn partner, kinderen of andere mantelzorgers betrokken werden		
Mijn partner, kinderen of andere mantelzorgers wilden niet betrokken worden of waren hier niet toe in staat		
Ik heb geen partner, kinderen of andere mantelzorgers		

Hoe kan uw zorg worden verbeterd?

Welke zorg en ondersteuning kunnen u helpen om uzelf zekerder te voelen op het gebied van uw gezondheid en welzijn?

Overige opmerkingen:

Hartelijk dank voor het invullen van deze vragenlijst.

APPENDIX 11A: MAUQ (PATIENT INTERVENTION ARM VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app was makkelijk in gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	Het was makkelijk voor mij om de app te leren gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De navigatie was consistent bij het bewegen tussen schermen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	De interface van de app stelde me in staat alle functies te gebruiken (zoals informatie invoeren, op herinneringen reageren, informatie bekijken) die de app aanbiedt.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
5.	Telkens als ik een fout maakte met de app, kon ik die makkelijk en snel herstellen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
6.	Ik hou van de interface van de app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
7.	De informatie in de app was goed georganiseerd, zodat ik gemakkelijk de informatie kon vinden die ik nodig had.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
8.	De app gaf me voldoende bevestiging en informatie om me te laten weten hoe mijn actie vorderde.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
9.	Ik voel me op mijn gemak als ik deze app in een sociale omgeving gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
10.	De hoeveelheid tijd die in het gebruik van deze app gaat zitten, is passend voor mij.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
11.	Ik zou deze app opnieuw gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
12.	Over het algemeen ben ik tevreden met deze app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
13.	De app zou nuttig zijn voor mijn gezondheid	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

	en welzijn.		
14.	De app heeft mijn toegang tot de gezondheidszorg verbeterd.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
15.	De app heeft me geholpen mijn gezondheid effectief te beheren.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
16.	Deze app heeft alle functies en mogelijkheden die ik ervan verwachtte.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
17.	Ik kon de app zelfs gebruiken wanneer de internetverbinding slecht of niet beschikbaar was.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
18.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te ontvangen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS

APPENDIX 11B: MAUQ (PATIENT CONTROL ARM VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app zou nuttig zijn voor mijn gezondheid en welzijn.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	De app heeft mijn toegang tot de gezondheidszorg verbeterd.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De app heeft me geholpen mijn gezondheid effectief te beheren.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te ontvangen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

APPENDIX 12: MAUQ (PROVIDER VERSION)

#	Stellingen	N.v.t.	1	2	3	4	5	6	7
1.	De app was makkelijk in gebruik.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
2.	Het was makkelijk voor mij om de app te leren gebruiken.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
3.	De navigatie was consistent bij het bewegen tussen schermen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
4.	De interface van de app stelde me in staat alle functies te gebruiken (zoals informatie invoeren, op herinneringen reageren, informatie bekijken) die de app aanbiedt.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
5.	Telkens als ik een fout maakte met de app, kon ik die makkelijk en snel herstellen.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
6.	Ik hou van de interface van de app.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS
7.	De informatie in de app was goed georganiseerd, zodat ik gemakkelijk de informatie kon vinden die ik nodig had.	<input type="checkbox"/>	ONEENS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	EENS

8.	De app gaf me voldoende bevestiging en informatie om me te laten weten hoe mijn actie vorderde.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
9.	Ik voel me op mijn gemak als ik deze app in een sociale omgeving gebruik.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
10.	De hoeveelheid tijd die in het gebruik van deze app gaat zitten, is passend voor mij.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
11.	Ik zou deze app opnieuw gebruiken.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
12.	Over het algemeen ben ik tevreden met deze app.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
13.	De app zou nuttig zijn voor mijn zorgpraktijk.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
14.	De app verbeterde mijn toegang tot het leveren van gezondheidsdiensten.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
15.	De app hielp me de gezondheid van mijn patiënten effectief te beheren.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
16.	Deze app heeft alle functies en mogelijkheden die ik ervan verwachtte.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
17.	Ik kon de app zelfs gebruiken wanneer de internetverbinding slecht of niet beschikbaar was.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS
18.	Deze mHealth-app biedt een aanvaardbare manier om zorgdiensten te verlenen, zoals toegang tot voorlichtingsmateriaal, het bijhouden van mijn eigen activiteiten en het uitvoeren van zelfbeoordelingen.	<input type="checkbox"/>	ONEENS <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> EENS

CONFIDENTIAL

APPENDIX 13: AE/SAE FORM

Subject ID:				AE number:	
Date of awareness: ____/____/____ (only to be completed in case of SAE)				Follow-up number (as applicable):	
Description of event	Start date and time ____/____/____ ____:____ (if applicable)	Outcome <input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Not yet recovered <input type="checkbox"/> Death	Action taken regarding study intervention <input type="checkbox"/> None <input type="checkbox"/> Temporarily interrupted <input type="checkbox"/> Stopped permanently <input type="checkbox"/> Other:	Investigator's	
				Seriousness	Severity
	Stop date and time ____/____/____ ____:____ (if applicable)		<input type="checkbox"/> None <input type="checkbox"/> Medication <input type="checkbox"/> Non-drug therapy <input type="checkbox"/> Further investigation performed <input type="checkbox"/> Other <input type="checkbox"/> Stop study due to AE	<input type="checkbox"/> NO <input type="checkbox"/> YES <i>If YES, tick all criteria that apply:</i> <input type="checkbox"/> Results in death ➔ Date of death: ____/____/____ <input type="checkbox"/> Is life-threatening <input type="checkbox"/> Results in permanent impairment <input type="checkbox"/> Requires or prolongs inpatient hospitalization ➔ Date of hospitalization: ____/____/____ ➔ Date of discharge: ____/____/____ <input type="checkbox"/> Medical or surgical intervention to prevent any of the outcomes above <input type="checkbox"/> Chronic disease <input type="checkbox"/> Led to fetal distress, fetal death, congenital abnormality or birth defect	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe

*Guidance for Sponsor: any SAE with a causal relationship to the IMD, comparator or procedure should be reported to the CA.

Report completed by:
 ____/____/____ (dd/mm/yyyy)

Signature: Date:

Report validated by Investigator:
 ____/____/____ (dd/mm/yyyy)

Signature: Date:

APPENDIX 14: DD FORM

Subject ID:		DD number: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up nbr:		Device i	
Event	Start date and time	Stop date and time	Origin of device deficiency	Action taken (Multiple actions possible, tick all applicable)	

Describe event or deficiency:	Start: ____/____/____	Stop: ____/____/____	<input type="checkbox"/> Mechanical <input type="checkbox"/> Electronic <input type="checkbox"/> Software <input type="checkbox"/> Other:	<input type="checkbox"/> None <input type="checkbox"/> Use of device temporarily interrupted <input type="checkbox"/> Visit termination <input type="checkbox"/> Resolved deficiency <input type="checkbox"/> Partially resolved <input type="checkbox"/> Other:
	Start time*: ____:____ (if applicable)	Stop time: ____:____ (if applicable)	Type of device deficiency <input type="checkbox"/> Use error <input type="checkbox"/> Inadequate instructions <input type="checkbox"/> Device malfunction <input type="checkbox"/> Unknown <input type="checkbox"/> Not applicable <input type="checkbox"/> Other:	
	<input type="checkbox"/> Unknown <i>*If onset time is unknown, enter time of first notice</i>	<input type="checkbox"/> Ongoing		

Report completed by:
 ____/____/____ (dd/mm/yyyy)

Signature: Date:

Report validated by Investigator:
 ____/____/____ (dd/mm/yyyy)

Signature: Date:

7.3 Annex 3: TWOBE regulatory and ethical approval Belgian authority



Federal Agency for Medicines and Health Products
Avenue Galilée - Galilleelaan 5/03
1210 BRUSSELS
www.famhp.be

DG PRE – R&D Division
Tel.: +32 (0)2 528 4000
e-mail: ct.rd@fagg-afmps.be

Catholic University Leuven/University Hospitals
Leuven (KU Leuven/UZ Leuven)
Hans Wildiers
Oude Markt 13
3000 Leuven
Belgium

Your letter from	Your reference	Our reference	Annex	Date
		CIV-22-06-039827- SM01 /1309438	2	<u>Cfr. digital signature</u>

Onderwerp
Titre de l'objet
Subject

Goedkeuring van een wijziging van een klinisch onderzoek op 29/11/2022
Approbation d'une modification d'une investigation clinique le 29/11/2022
Authorization of a modification of a clinical investigation dated 29/11/2022

Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients (GerOnTe) – TWOBE.

Eudamed: CIV-22-06-039827

Substantial modification number: SM01

Chère Madame, Cher Monsieur,

Conformément au règlement (UE) 2017/745 sur les dispositifs médicaux, il a été décidé d'autoriser l'investigation clinique mentionnée ci-dessus. Cette autorisation est le résultat d'avis favorables émis par l'AFMPS et un comité d'éthique désigné par le Collège en accord avec la loi du 22 décembre 2020. La liste des documents sur laquelle la décision est basée et la liste des sites et investigateurs approuvés sont en annexe de cette approbation.

Geachte Mevrouw, Geachte Heer,

In overeenstemming met de verordening (EU) 2017/745 betreffende medische hulpmiddelen werd er besloten het bovenvermeld klinisch onderzoek goed te keuren. Deze goedkeuring is het resultaat van de gunstige adviezen verleend door het FAGG en het Ethisch Comité aangewezen door het College volgens de wet van 22 december 2020. De lijst van documenten waarop deze beslissing is gebaseerd en de lijst van goedgekeurde sites en onderzoekers bevinden zich in bijlage van deze goedkeuring.

Sincères salutations,

Hugues Malonne
Directeur général – DG PRE Autorisation
Délégué du Ministre de la santé Publique

Met de meeste hoogachting,

Hugues Malonne
Directeur-generaal – DG PRE Vergunning
Afgevaardigde van de Minister van
Volksgezondheid



Digitally signed by: Hugues Malonne (Signature)
DN: CN = Hugues Malonne (Signature) C = BE
Date: 2022.12.14 22:16:29 +01'00'

Unofficial translation

In accordance with the regulation (EU) 2017/745 on medical devices it was decided to authorize the above mentioned clinical investigation. This decision is the result of the advice issued by the FAMHP and an Ethics Committee designated by the College in line with the law of 22 December 2020. The list of documents on which the opinion was based and a list with approved sites and principal investigators can be found in annex.

Annex I

List of documents on which the advices are based

Documents	Version and/or date
COVER LETTER	
GerOnTe TWOBE_Cover Letter_v0.1_20221104.pdf	V0.1 - 04/11/2022
APPLICATION FORM SUBSTANTIAL MODIFICATION	
GerOnTe TWOBE_Substantial Modification_AF_v0.1_20221104.pdf	V0.1 - 04/11/2022
MODIFIED DOCUMENTS	
/	/
SUPPORTING INFORMATION (if any)	
AEZ_1306353-CIV-22-06-039827_Approval	05/10/2022

Annex II

List of approved sites and investigators for the clinical investigation:

- Trial site 1 – UZ Leuven
Investigator 1 – Prof. Dr. Hans Wildiers
- Trial site 2 – UZ Brussel
Investigator 2 – Prof. Dr. Lore Decoster
- Trial site 3 – AZ Sint Jan
Investigator 3 – Dr. Barbara Brouwers
- Trial site 4 – AZ Groeninge
Investigator 4 – Prof. Dr. Philip Debruyne

7.4 Annex 4: TWOBE regulatory and ethical approval Dutch authority



Medical research Ethics
Committees United

Postbus	Postbus 2500 3430 EM Nieuwegein
Bezoekadres	Koekoekslaan 1 te Nieuwegein 088 320 8784
E-mail	info@mec-u.nl
Website	www.mec-u.nl

Universitaire Ziekenhuizen Leuven
Afdeling Medische Oncologie
Prof. Dr. H.P.M.W. Wildiers
Herestraat 49
3000 LEUVEN, BELGIË

Betreft: besluit **R22.056**
NL81897.100.22

Datum: 11-11-2022

Geachte heer Wildiers,

Hierbij ontvangt u het besluit van MEC-U over uw onderzoeksvoorstel getiteld: "*Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients - TWOBE study*" en ons registratienummer **R22.056**.

MEC-U verleent haar goedkeuring aan het onderzoek. De goedkeuring betreft de uitvoering in het besluit vermelde centra.

Zie het bijgevoegde besluit voor de overwegingen bij het besluit.

Wij maken u erop attent dat *voordat* het onderzoek van start gaat, een getekend exemplaar van de goedgekeurde versie van het onderzoekscontract ter kennisgeving bij ons moet worden ingediend.

MEC-U wijst u erop dat definitieve toestemming van de Raad van Bestuur van de deelnemende centra nodig kan zijn voordat tot uitvoering van het onderzoek kan worden overgegaan.

Jaarlijkse bijdrage

Naast de beoordelingskosten voor de primaire indiening en eventuele amendementen zal er aan externe partijen, nadat het primaire besluit is afgegeven, jaarlijks een abonnementstarief in rekening worden gebracht gedurende de looptijd van de studie.

Meer informatie hierover is te vinden op de website www.mec-u.nl, onder het kopje 'Tarieven'.

Wij vertrouwen erop u hiermee voldoende te hebben geïnformeerd.

Met vriendelijke groet,
secretariaat MEC-U

Deelnemende instellingen: St. Antonius Ziekenhuis te Utrecht/Nieuwegein/Woerden, Catharina Ziekenhuis te Eindhoven, Diaconessenhuis te Utrecht/Zelst/Doorn, Maasstad Ziekenhuis te Rotterdam, Meander Medisch Centrum te Amersfoort/Baarn, Medisch Spectrum Twente te Enschede, OLVG te Amsterdam en Ziekenhuisgroep Twente te Almelo/Hengelo.

BESLUIT
Primaire beoordeling

NL-nummer	NL81897.100.22	Registratienr.	R22.056
Titel onderzoek	Streamlined Geriatric and Oncological evaluation based on IC Technology for holistic patient-oriented healthcare management for older multimorbid patients - TWOBE study		

Contactgegevens: UZ Leuven, afdeling Medische Oncologie, prof. dr. H.P.M.W. Wildiers, Herestraat 49, 3000 Leuven (BE).
Verrichter: UZ Leuven te Leuven (BE)

Besluit

Het bovenstaande aanvraagdossier betreft een onderzoek als bedoeld in artikel 82 van Verordening (EU) 2017/745 (hierna: de verordening).

De medisch-ethische toetsingscommissie MEC-U heeft zich, op grond van artikel 62, vierde lid, onder b, van de verordening juncto artikel 2, tweede lid, aanhef en onder a, van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO), beraden over het dossier.

De commissie oordeelt positief over het aanvraagdossier uit te voeren in de volgende centra:

- Catharina Ziekenhuis te Eindhoven, hoofdonderzoeker dr. B.E.P.J. Vriens
- Diaconessenhuis te Utrecht, hoofdonderzoeker dr. M.E. Hamaker
- Leids Universitair Medisch Centrum Leiden, hoofdonderzoeker dr. F. van der Bos
- Reinier de Graaf Gasthuis te Delft, hoofdonderzoeker dr. J.M van der Bol.

Documenten

Het besluit is gebaseerd op de documenten die in bijlage 1 staan vermeld.

Achtergrond

Op 28-06-2022 is het aanvraagdossier ter beoordeling bij MEC-U ingediend. Het dossier is besproken in de plenaire vergadering(en) van MEC-U op 11-07-2022 en 11-11-2022 (zie bijlage 2 voor de aanwezige leden op 11-07-2022).

Op een vraagbrief en/of verzoek om aanvullende informatie vanuit MEC-U van 14-07-2022, 22-09-2022 en 31-10-2022 is door de indiener gereageerd op 26-08-2022, 26-10-2022 en 09-11-2022.

Overwegingen

De commissie is van oordeel dat aan de voorwaarden in artikel 62, vierde lid, onder c, f, h en l, van de verordening is voldaan. Daarnaast is zij van oordeel dat aan de voorwaarden in artikel 3, eerste lid, onder b, c, e t/m h en l, van de WMO is voldaan. De belangrijkste hadden betrekking op:

- De werking van de software; doet deze meer dan registreren en zo ja kan de onderzoeker de evolutie van het AI-algoritme volgen, wat is het lerende aspect in deze toepassing en op welke parameters wordt er geoptimaliseerd?
- De samplesize berekening en het gekozen design (stepped wedge cross-over design);
- De inhoud van de proefpersoneninformatie;
- Verduidelijking ten aanzien van de CE-markering van het medisch hulpmiddel;
- Document specifieke vragen (ABR-formulier, IB, IMDD en het onderzoekscontract).

Besluit MEC-U R22.056 (NL-nummer NL81897.100.22)

Deelnemende instellingen: St. Antonius Ziekenhuis te Utrecht/Nieuwegein/Woerden, Catharina Ziekenhuis te Eindhoven, Diaconessenhuis te Utrecht/Zeist/Doorn, Maasstad Ziekenhuis te Rotterdam, Meander Medisch Centrum te Amersfoort/Baarn, Medisch Spectrum Twente te Enschede, OLVG te Amsterdam en Ziekenhuisgroep Twente te Almelo/Hengelo.



De belangrijkste argumenten van de commissie om over te gaan tot een positief besluit zijn dat de vragen genoegzaam zijn beantwoord en de documenten correct zijn aangepast.

De commissie heeft de in bijlage 1 vermelde onderzoeksverklaringen bekeken. Zij heeft geconstateerd dat is voldaan aan de voorwaarden in artikel 62, zesde lid, van de verordening. Daarnaast is zij van oordeel dat is voldaan aan de voorwaarden in artikel 3, eerste lid, onder f, van de WMO.

De commissie is van oordeel dat het onderzoeksprotocol in een informatie- en toestemmingsprocedure voorziet die overeenstemt met artikel 63 van de verordening.

Meer specifiek is de commissie van mening dat is voldaan aan de voorwaarden in artikel 63, tweede lid, van de verordening. De schriftelijke informatie die aan de proefpersonen [en/of aan de wettelijke vertegenwoordiger van de proefpersonen] wordt gegeven om hun geïnformeerde toestemming te verkrijgen is volledig, beknopt, duidelijk, relevant en begrijpelijk voor hen. Daarnaast heeft de commissie geconstateerd dat de proefpersonen zich te allen tijde uit het onderzoek kunnen terugtrekken zoals bepaald in artikel 6, negende lid, van de WMO.

Verzekeringen

MEC-U heeft geconstateerd dat is voldaan aan de verzekeringsplicht. Er is een proefpersonenverzekering afgesloten zoals bepaald in artikel 7, eerste lid, van de WMO en zoals nader uitgewerkt in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015 (Besluit van 24 november 2014). Het onderzoek valt onder de proefpersonenverzekering van Stichting Diaconessenhuis Utrecht.

De commissie heeft geconstateerd dat een aansprakelijkheidsverzekering is afgesloten zoals bepaald in artikel 7, negende lid, van de WMO.

Het is de verantwoordelijkheid van de verwerkingsverantwoordelijke(n) om aan de privacyregels zoals die volgen uit de Algemene Verordening Gegevensbescherming en de Uitvoeringswet Algemene Verordening Gegevensbescherming te voldoen. Het is aan de Autoriteit Persoonsgegevens om genomen maatregelen al dan niet (achteraf) te toetsen.



4/9

Ten slotte wijst MEC-U u op de voorwaarden en verplichtingen die in bijlage 3 staan vermeld.

Met vriendelijke groet,



Mw. drs. M.M.E. van Dijk-Baak, ambtelijk secretaris

Namens dr. R.J.E. Grouls
voorzitter Medical research Ethics Committees United (MEC-U)

Nieuwegein, 11-11-2022

Beroepsprocedure

Tegen dit besluit kan een belanghebbende op grond van artikel 23 van de WMO binnen zes weken na de dag waarop het besluit is bekend gemaakt, administratief beroep instellen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO). Het beroepschrift dient u te adresseren aan CCMO, Postbus 16302, 2500 BH Den Haag.

Besluit MEC-U R22.056 (NL-nummer NL81897.100.22)

Deelnemende instellingen: St. Antonius Ziekenhuis te Utrecht/Nieuwegein/Woerden, Catharina Ziekenhuis te Eindhoven, Diaconessenhuis te Utrecht/Zeist/Doorn, Maasstad Ziekenhuis te Rotterdam, Meander Medisch Centrum te Amersfoort/Baarn, Medisch Spectrum Twente te Enschede, OLVG te Amsterdam en Ziekenhuisgroep Twente te Almelo/Hengelo.

Bijlage 1

Documenten

Secctie	Onderwerp	Versie
A1	begeleidende e-mail bij indiening	d.d. 27-06-2022, e-mail zonder bijlagen
A1	begeleidende e-mail bij indiening	d.d. 28-06-2022 (met bijlage ABR-formulier)
A1	begeleidende e-mail bij indiening	d.d. 28-06-2022 WeTransfer
A1	aanbiedingsbrief	d.d. 24-06-2022
A1	correspondentie tussen MEC-U en indiener: vraagmail	d.d. 14-07-2022
A1	begeleidende e-mail bij indiening	d.d. 26-08-2022
A1	correspondentie tussen MEC-U en indiener: reactiebrief indiener	d.d. 26-08-2022
A1	correspondentie tussen MEC-U en indiener: vraagmail	d.d. 22-09-2022
A1	begeleidende e-mail bij indiening	d.d. 26-10-2022
A1	correspondentie tussen MEC-U en indiener: reactiebrief indiener	d.d. 26-10-2022
A1	correspondentie tussen MEC-U en indiener: vraagmail	d.d. 31-10-2022
A1	begeleidende e-mail bij indiening	d.d. 09-11-2022
A1	correspondentie tussen MEC-U en indiener: reactiebrief indiener	d.d. 04-11-2022
B1	ABR-formulier	versie 04 d.d. 03-11-2022
C1	onderzoeksprotocol	versie 02 d.d. 10-10-2022
D1	IB (Investigator's Brochure)	benefit risk ratio, versie 0.1 d.d. 18-10-2022
D1	IB (Investigator's Brochure)	Holis-5.2_Benefit risk ratio, versie en datum ontbreken
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure versie 1 d.d. 08-06-2022
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_A, datum ontbreekt
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_B
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_C, versie 1.4 d.d. 07-03-2022
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_D versie 1.3 d.d. 10-03-2022
D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_E versie 1.0 d.d. 23-04-2022

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D1	IB (Investigator's Brochure)	Holis-InvestigatorBrochure_Attachment_F versie 1 d.d. 25-03-2022
D2	IFU (instructions for use)	Holis versie 1 d.d. 24-05-2022
D2	IFU (instructions for use)	Holis versie 1 d.d. 25-03-2022
D2	IMDD	Holis versie 1 d.d. 25-03-2022
D2	IMDD	Holis-Small scale pilots report versie 1.0 d.d. 23-04-2022
D2	IMDD	Holis, versie 0.3 d.d. 18-10-2022
D2	overige productinformatie	beschrijving medical device, versie 2 d.d. 26-08-2022
D2	overige productinformatie	veiligheidscontrole MyPL
D2	overige productinformatie	verklaring afwezigheid CE-markering d.d. 29-03-2022
D4	vergunning/verklaring	Statement of conformity d.d. 25-03-2022
E1-2	proefpersoneninformatie incl. toestemmingsformulier	mantelzorger, versie 02 d.d. 10-10-2022
E1-2	proefpersoneninformatie incl. toestemmingsformulier	patiënt controle, versie 02 d.d. 10-10-2022
E1-2	proefpersoneninformatie incl. toestemmingsformulier	patiënt interventie, versie 02 d.d. 10-10-2022
E1-2	proefpersoneninformatie incl. toestemmingsformulier	zorgverlener, versie 02 d.d. 10-10-2022
G1	certificaat WMO-proefpersonenverzekering	Diaconessenhuis Utrecht bij Centramed d.d. januari 2022 (polisnr. 624.100.016)
G2	bewijs dekking aansprakelijkheid	Diakonessenhuis Utrecht bij Centramed d.d. januari 2022 (polisnr. 624.100.016)
H1	cv onafhankelijk deskundige	dr. T.J.M. Tobé
H2	BROK/GCP-certificaat coördinerend onderzoeker	H. Wildiers d.d. 01-07-2021
H2	cv coördinerend onderzoeker	prof.dr. H.P.M.W. Wildiers
I1	lijst deelnemende centra	versie en datum ontbreken
I2	onderzoeksverklaring	Catharina Ziekenhuis d.d. 30-03-2022
I2	onderzoeksverklaring	Diakonessenhuis Utrecht d.d. 24-03-2022
I2	onderzoeksverklaring	Leids Universitair Medisch Centrum d.d. 14-04-2022
I2	onderzoeksverklaring	Reinier de Graaf Groep d.d. 15-04-2022
I3	cv hoofdonderzoeker	Catharina Ziekenhuis, dr. B.E.P.J. Vriens d.d. 29-03-2022
I3	cv hoofdonderzoeker	Diakonessenhuis Utrecht, dr. M.E. Hamaker
I3	cv hoofdonderzoeker	Reinier de Graaf Groep, dr. J.M. van der Bol

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I3	cv hoofdonderzoeker	Leids Universitair Medisch Centrum, dr. F. van den Bos fd.d. 12-04-2022
I3	GCP-certificaat hoofdonderzoeker	B. Vriens d.d. 15-03-2021
I3	GCP-certificaat hoofdonderzoeker	F. van den Bos d.d. 05-06-2018
I3	GCP-certificaat hoofdonderzoeker	J.M. van der Bol d.d. 12-04-2022
I3	GCP-certificaat hoofdonderzoeker	M. Hamaker d.d. 11-05-2021
K2	overzicht buitenl. beoordelingen/bevoegde instanties	GerOnTe TWOBE
K3	onderzoekscontract DRAFT	tussen Universitaire Ziekenhuizen Leuven en [instelling] versie en datum ontbreken
K6	brief aan huisarts	versie 00 d.d. 10-10-2022

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Bijlage 2

Samenstelling MEC-U

De volgende leden waren aanwezig tijdens de commissievergadering van 11-07-2022:

- dr. R.J.E. Grouls, voorzitter
- ir. A.J. Arends, klinisch fysicus
- dr. M. Groeneweg, kinderarts
- dhr. G. van den Hoogen, proefpersonenlid
- mr. E. Hulst, jurist
- dr. J.C. Kelder, methodoloog
- dr. H.E.M. van Luijn, ethicus
- dr. A.M.J. Thijs, arts

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Bijlage 3

Voorwaarden en verplichtingen

Geldigheid oordeel

Het positieve oordeel verliest zijn geldigheid als de inclusie van de eerste proefpersoon niet heeft plaatsgevonden binnen twee jaar nadat dit besluit is genomen.

Amendementen

Amendementen dienen ter beoordeling aan MEC-U te worden voorgelegd.

Startdatum onderzoek

MEC-U dient op de hoogte te worden gesteld van de definitieve startdatum van het onderzoek. Dat is de datum waarop de inclusie van de eerste proefpersoon plaatsvindt.

Voortgangsrapportage

Eén jaar na datum van het oordeel, en ieder jaar daaropvolgend, dient de METC op de hoogte te worden gebracht van de voortgang van de studie middels het formulier Voortgangsrapportage.

Geldigheid verzekering

In het geval het verzekeringscertificaat tijdens de voortgang van het onderzoek zijn geldigheid verliest, dient aan MEC-U tijdig een afschrift van een nieuw geldig certificaat te worden toegestuurd.

Melding SAE's

Indien van toepassing dienen SAE's aan MEC-U te worden gemeld.

Melding (voortijdige) beëindiging en opschorting

(Voortijdige) beëindiging en opschorting van het onderzoek dient, met redenen omkleed, te worden gemeld aan MEC-U.

Eindrapportage

MEC-U dient op de hoogte te worden gebracht van de resultaten van het onderzoek middels een eindrapport.

Termijnen en overige uitleg ten aanzien van de indiening van de verschillende documenten aan MEC-U vindt u op de website van de CCMO.



www.geronteproject.eu



contact@geronteproject.eu



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