STREAMLINED **GER**IATRIC AND **ON**COLOGICAL EVALUATION BASED ON IC **TE**CHNOLOGY
FOR HOLISTIC PATIENT-ORIENTED HEALTHCARE MANAGEMENT
FOR OLDER MULTIMORBID PATIENTS

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History of Changes

Version	Date	Author	Description of change
V1.0	2022-03-31	Cecile Duchiron [UBx]	First version
V2.0	2023-02-01	Lien Degol [KUL]	Modifications following the expert opinion

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Executive Summary

Deliverable work status

Deliverable	Completion status in %	Deviation	Data complete or to be updated
D4.1 Clinical trial methodology	100%	Deviation of content *(see 'Attainment of the objectives and explanation of deviations')*	Data complete
Associated Deliverables	D4.3 First study subject approvals package for FRONE D4.4 First study subject approvals package for TWOBE		
Associated Objectives	O4 Demonstrate in 16 study sites from three EU countries the feasibility and effectiveness of the GerOnTe model		

Description of deliverable

This deliverable is a summary of the clinical trial methodology that will be included in the final version of the FRONE and TWOBE trial protocol.

This deliverable is connected to D4.3 First study subject approvals package for FRONE and D4.4 First study subject approvals package for TWOBE. This summary of the clinical trial methodology will be included in the final version of the FRONE and TWOBE trial protocol as part of the approvals packages.

The deliverable is associated to O4 Demonstrate in 16 study sites from three EU countries the feasibility and effectiveness of the GerOnTe model. D4.1 briefly describes the methodology of the FRONE and TWOBE clinical trials. Proof of concept will be done in these two clinical trials in three EU countries, namely France, Belgium and the Netherlands, using the clinical trial methodology described in D4.1.

Attainment of the objectives and explanation of deviations

Attainment of the objectives

The objectives related to this deliverable have been achieved in full, but modifications were made to the content of D4.1 as described in Annexe 1 (Description of the Action Part A) of the Grant Agreement N°945218. The deviations in D4.1 will be explained in the section below.

Explanation of deviations

For D4.1, 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.

New timeline for tasks and deliverables for WP4:

Task:	Description	Leader	Participants	Start	End
4.1	Coordination of the clinical trials	UBX	UBX, KUL, DIAK, MYPL, BOC, DCU	1	56
4.2	Clinical trial compliance to ethical and regulatory requirements	UBX	UBX, KUL, DIAK	1	19
4.3	Enrolment of participants in the three participating countries (16 clinical sites)	UBX	UBX, KUL, DIAK	29	38

4.4	Clinical trial data collection and management	UBX	UBX, KUL	M28	56
4.5	Statistical analysis and final statistical report	UBX	UBX, KUL, DIAK, BOC, DCU	M28	60
MS5	Recruitment of at least 500 patients for the correct analysis of RCT outputs				M42

Deliverables	Description	Delivery date
D4.1	Clinical trial methodology	M12
D4.2	Trial committees' charters	M12
D4.3	First study subject approvals package for FRONE	M18, update M25
D4.4	First study subject approvals package for TWOBE	M18, update M26
D4.5	Mid-term recruitment report for FRONE	M36
D4.6	Mid-term recruitment report for TWOBE	M36
D4.7	Full-term recruitment report for FRONE	M46
D4.8	Full-term recruitment report for TWOBE	M46
D4.9	eCRF collection complete database	M56
D4.10	statistical analysis plan	M22, Update M26
D4.11	statistical analysis report	M60
D4.12	Status of posting results for FRONE	M60
D4.13	Status of posting results for TWOBE	M60

Justification for delay in deliverable submission

The objectives related to this deliverable have been achieved on time and as scheduled in Annexe 1 (Description of the Action Part A) of the Grant Agreement N°945218.

Glossary

ADL	Activities of Daily Living scale
APN	Advanced Practice Nurse
EORTC	European Organisation for Research and Treatment of Cancer
HAD	Hospital Anxiety and Depression scale
ITT	Intention To Treat
MTB	Multidisciplinary Tumor Board
PFS	Progressive Free Survival
SNDS	National Health Data System

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 (Holis^{TM}) 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

O1: INFORMATION gather the stakeholders and data needed for patient-centred and multi-actor complex decision-making process and management

O2: **TOOLS** develop ICT tools for the GERONTE intervention to be implemented

O3: METHODS develop socio-economic methods for evaluating the impacts of the implementation of the GERONTE intervention

O4: **DEMONSTRATION** demonstrate in 16 study sites from three EU countries the feasibility and effectiveness of the GERONTE intervention

O5: **REPLICATION** develop recommendations for the replication of GERONTE best practices in all European health systems

O6: ENGAGEMENT engage all stakeholders by co-designing the GERONTE intervention

1.2. Rationale

The current work corresponds to deliverable D4.1, which is part of work-package 4 which supports GERONTE objective 3 "Demonstration and validation". 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.

2. Study objectives

2.1. Primary objective

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

2.2. Secondary objectives

The secondary objectives of GerOnTe trials are, in the context of a French health-system organization for FRONE and in the Belgium and Dutch health-system context for TWOBE, to:

- Evaluate the effectiveness of the GerOnTe patient-centered 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 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 unplanned hospitalizations and patient institutionalizations at 6 and 12 months (secondary endpoint #5);
- Evaluate the efficiency of the GerOnTe patient-centered system through a cost-utility analysis. The medico-economic analysis will focus on the entire care pathway from the beginning of patient management with the GerOnTe system 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 after patient inclusion (secondary endpoint #7);
- Evaluate patient-reported overall experience of the GerOnTe system at 6 and 12 months' post-inclusion (secondary endpoint #8);
- Evaluate patient and health professionals reported overall satisfaction and acceptability of GerOnTe system at 6 and 12 months (secondary endpoint #9);
- Analyze the implementation and use of the GerOnTe patient-centred system by patients and professionals (secondary endpoint #10).
- Ancillary studies

3. Study endpoints

3.1. Primary endpoint

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

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

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

Normalised 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

- Normalised scores of global health status, physical functioning scale and emotional functioning scale of the QLQ-C30 (version 3.0) questionnaire collected at 3, 9 and 12 months after inclusion;
- Normalised Scores of the following QLQ-C30 scales/items assessed at 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 assessed at 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-LD14 questionnaire is a complementary module to the QLQ-C30 and taking into account the specific needs of elderly 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

- Dependence score of the Activities of Daily Living scale (ADL) assessed at 3, 6, 9 and 12 months after inclusion;
- Proportion of patients living at home 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).
- Clinical frailty scale

4. Patient anxiety

Score of HAD scale at 3, 6, 9 and 12 months after inclusion.

5. Patient institutionalization and unplanned hospitalizations

- Proportion of patients in nursing home at 6 and 12 months after inclusion.
- Proportion of unplanned hospitalisations during 12 months after inclusion.

6. Cost-utility

- Cost-utility ratio at 3, 6, 9 and 12 months
  - Utility assessed through normalised scores of EQ-5D-5L questionnaire collected at baseline, at 3, 6, 9 and 12 months after inclusion. It includes the 5-level questions covering five domains: mobility, self-care, usual activities, pain and discomfort, anxiety and depression.
    - Resource use data during the 12 months of patient follow-up will include all direct and indirect costs. Resource use data directly spurred by patient management collected through the medical-administrative databases of the SNDS (National Health Data System) linked to the patient sample by deterministic matching.

- Cost of hospitalisation;
- Pharmaceutical consumption;
- Outpatient attendance;
- Emergency department access;
- Nursing home care and access to other healthcare facilities;

– Resource use data collected through micro costing
  - Labor costs (salary, over-time, welfare and other compensation);
  - Unpaid caregivers' labor (informal care, community care, or unpaid caregivers' time);
  - Patient or caregiver non-productive leisure time (time that patients or caregiver give up during treatment and convalescence);
  - Time spent by health professionals to manage the patients.

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 at al 2017] 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-centered coordinated care

Patient experience measured through the Person-Centered Coordinated Care Experience Questionnaire (P3CEQ) - 10 items (Lloyd et al 2019) at 6 and 12 months after inclusion.

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

Patient satisfaction and usability of mHealth application within GerOnTe system will be analysed through the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Patient version), a 21-item scale (Zhou et al 2019) at 6 and 12 months after inclusion.

The adjusted version designed for health care providers of the mHealth App Usability Questionnaire (MAUQ) for standalone mHealth Apps (Provider version), a 21-item scale (Zhou et al 2019) will be used to evaluate physician and health-professional overall statisfaction at 6 months.

10. GerOnTe patient-centered system implementation and usage

GerOnTe patient-centered system implementation and usage will be evaluated at 6 months after inclusion (2 and 4 months for the two last centers implementing GerOnTe system):

– Number and frequency of connections to the Holis^{TM} GV app by patients;
– Duration of logins and activities with the Holis^{TM} GV app by patients;
– Number of web-based meetings with APN by site;
– Number of APN consultations by site (and by patient) and kind of interventions/actions taken;
– Number of PROM's dashboards completed by participant;
– Number of health professional meetings (Multidisciplinary Tumour boards (MTB) or other morbidities treatment decision) involving complete dashboards analysis by site.

11. Ancillary studies

Ancillary studies are fully described in Appendix 1 of the protocol.

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 have implemented 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 center; 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 center has to stop the inclusions till the beginning of the subsequent step. If a center, near to the end of a step, is far from reaching the 10 patients included, it must increase the speed of its inclusions to be as close as possible to 10 patients included at the end of the step. In each center, patient sample has to be representative of the type(s) of cancer managed in the center, along the trial duration. The repartition of cancer types must be homogeneous along the steps and during the trial duration.

At all participating investigating sites, dedicated study collaborators will be 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 center committed to participate needs to participate till the end of the trial; no center withdrawal is allowed during the trial.

Quantitative data regarding the Holis^{TM} GV home app usage will be collected at each step and in each cluster by study collaborators, from the beginning of GerOnTe system implementation. Care outcome data (Quality of life, anxiety, autonomy, additional hospitalisation, mortality...) will be collected by local referents 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-centered system implementation and usage will be collected by the local referents in each center. Qualitative analysis will be performed in each center at GerOnTe system implementation and during follow-up.

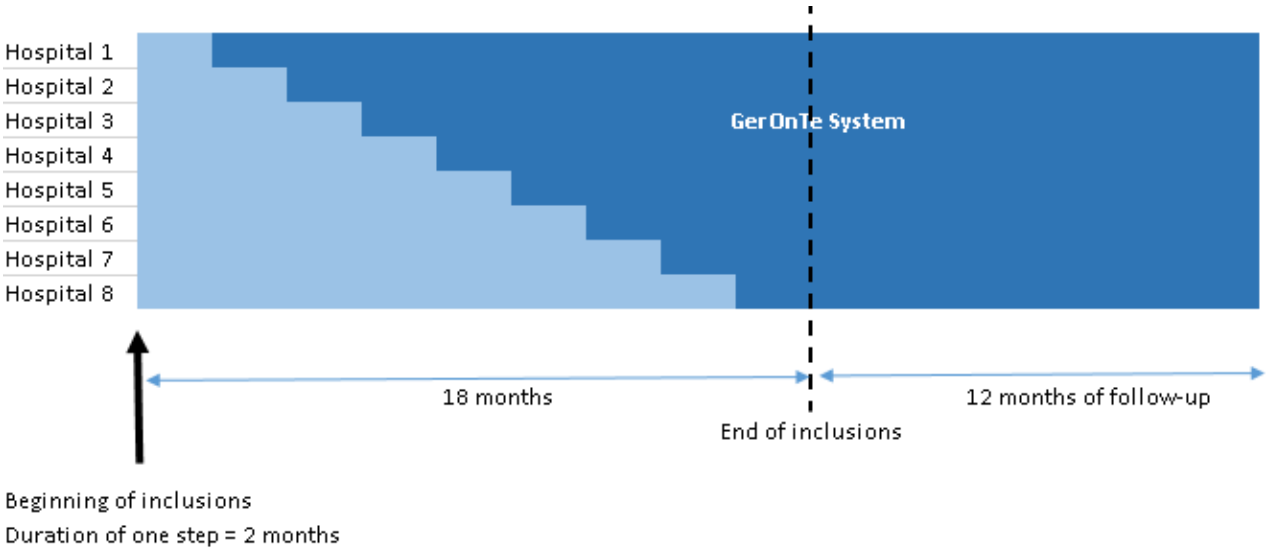

Figure 2: Schematic representation of FRONE stepped wedge cross-designed for inclusion of 720 patients across eight sites per trial.

The randomisation list will be established by the statistician at the Methodology and Data Management Centre (EUCLID) 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.

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 18 months of active enrollment.

Planned start date (first participant on study): September 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 or in the intervention arm.

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

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

If funding permits, a follow-up of patients up to five years after protocol inclusion will be planned. Minimal data will be collected from patient's chart including relapse or progression, survival and institutionalisation.

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 with 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. Statistical considerations

5.1. Hypotheses and number of participant 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), 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 par step and per centre (Table 2.1)

Randomised investigating sites	Number of patients to be included **per step on average**	Total Nb of patients to be included **control arm**	Total Nb of patients to be included **Intervention arm**	Total nb of patients to be included – 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-to-follow-up will be, in particular, excluded)

5.2. Hypotheses and number of participants needed

5.2.1. 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 per treatment group.

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

5.2.2. Statistical method

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.

5.2.3. Analysis plan

A detailed statistical analysis plan will be developed Q4 2022 and submitted as deliverable D4.10.

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