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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D4.3: First study subject approvals package for FRONE

Lead Beneficiary : 1-UBX

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

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History of Changes

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V1.0	2022-09-29	Pierre Soubeyran [UBX]	First version
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V3.0	2023-05-31	Lien Degol [KUL]	Update at M26

Table of Content

Executive Summary	5
1. Introduction	9
1.1. GERONTE and its objectives	9
1.2. Rationale	10
2. Clinical trial protocol	11
3. Regulatory approval	11
4. Ethical approval	11
5. Trial registration	11
6. Conclusion	11
7. Annexes	12
7.1 Annexe 1: FRONE clinical trial protocol	12
7.2 Annexe 2: FRONE regulatory approval	102
7.3 Annexe 3: FRONE ethical approval	104

Executive Summary

Deliverable work status

Deliverable	Completion status in %	Deviation	Data complete or to be updated
D4.3 First study subject approvals package for FRONE	75% at M18 100% at M26	Deviation of content and deviation of timeline *(see 'Justification for delay in deliverable submisision')*	Data complete
Associated Deliverables	D4.3 First study subject approvals package for FRONE		
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 FRONE, it will include the final version of the FRONE trail protocol, the registration number of the clinical trial (clinicaltrials.gov) and the regulatory and/or ethics approvals.

This deliverable is connected to D4.4 First study subject approvals package for TWOBE. The research protocol is first developed for clinical trial FRONE considering the French regulations, 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 version of the FRONE trial protocol as well as the regulatory approval for the FRONE clinical trial. 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 FRONE and the registration of the trial at clinicaltrials.gov.

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.

Justification for delay in deliverable submission

A delay in D4.3 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 Tri3al 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 (see Task 4.2 Clinical trial compliance with ethical and regulatory requirements).
f. Establishing which category the trial should be submitted to in France, 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. Delay in recruitment of centres in France:
    a. The identification of clinical sites in France required a feasibility assessment. In view of the complexity of the study and the regulations on the protection of patient health data, some centres that initially planned to participate in the study withdrew because of feasibility questions such as their capacity to enroll 10 patients per 2 months and to ensure the availability of the Advanced Practice Nurse (APN). 8 centres were pre-selected. Of the 8 centres initially selected, 2 withdrew and 3 were excluded after further discussions. The selection process had to be repeated to replace the 5 centres. 6 centres were contacted: 5 were retained and there is now 1 centre in the queue.
    b. For FRONE, the centres that will participate in the study should be as similar as possible to the French health system. We must have public and private centres, reference centres in urban and rural areas so that the distribution of patients recruited is as homogeneous as possible in relation to the whole French population.
3. Clinical trial registration delay in FRONE:
    a. Per Institut Bergonié procedures, the registration of the study on clinicaltrials.gov website has to be done after authorisation form the competent authorities, which is not necessarily the case in other countries or hospitals. This procedure was put in place to avoid registering studies that will never start because they did not receive the necessary authorisations. The delay due to the necessary regulatory submission had a direct impact on this registration. Authorisations from the competent authority (ANSM) and Ethics Committee (CPP) were received in September 2022. Registration was then initiated internally but was only started in January 2023 on the website. The delay in registering the study on this clinical site has no impact on the progress of further activities.
4. 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 evey 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 along 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

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

Deliverable D4.3 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 FRONE clinical trial protocol can be found in Annexe 1.

3. Regulatory approval

The written regulatory approval of Agence Nationale de Sécurité du Médicament (ANSM) for FRONE can be found in Annexe 2.

4. Ethical approval

The written ethical approval of Comités de Protection des Personnes (CPP) for FRONE can be found in Annexe 3.

5. Trial registration

The clinical trial GerOnTe FRONE is registered on February 9, 2023 in ClinicalTrials.gov with registration number NCT05720910.

6. Conclusion

This deliverable is the study approvals package for FRONE, this first version of the package delivers in the annexes, the latest version of the FRONE trial protocol as well as the regulatory approval for the FRONE clinical trial. This update includes also the ethical approval for FRONE as well as the registration of the trial at clinicaltrials.gov.