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CHANGE HISTORY

Ver.	Date	Status	Author (Beneficiary)	Description
1.1	23/06/16	Draft	Marina Kotsani (INSERM)	First Draft
1.2	24/06/16	Draft	Athanase Benetos(INSERM)	Several Revisions
1.3	27/06/16	Draft	Jirar Topouchian (INSERM)	Incorporation of comments
1.4	27/06/16	Draft	Kosmas Petridis (HYPERTECH)	Review and incorporation of comments
1.5	27/06/16	Draft	Kyriakos Sgarbas (UoP)	Incorporation of review comments, second draft
1.6	27/06/16	Draft	Ioanna Petridou (MATERIA GROUP)	Translation and incorporation of a questionnaire
1.7	28/06/16	Draft	Roberto Orselli (SMARTEX)	Review and incorporation of comments
1.8	28/06/16	Draft	Eirini Tsiamaki (UoP)	Incorporation of paragraphs, third draft
1.9	29/06/16	Draft	Vasilis Megalooikonomou (UoP)	Review, comments and suggestions
1.10	29/06/16	Draft	Marina Kotsani (INSERM)	Incorporations of all partners' revisions, forth draft
1.11	29/06/16	Draft	Athanase Benetos(INSERM)	General review
1.12	30/06/16	Final	Marina Kotsani (INSERM)	Final version
2.1	12/12/16	Revision Draft	Yannis Elloul (UoP)	First approach to revision
2.2	13/12/16	R. Draft	Marina Kotsani (INSERM) and many consortium members	Modifications to first approach
2.3	21/12/16	R. Draft	Yannis Elloul (UoP), Athanase Benetos (INSERM), Marina Kotsani (INSERM)	Additions, comments, suggestions, answer to reviewers' comments

2.4	26/12/16	R. Draft	Marina Kotsani (INSERM)	Incorporation of consortium's oral and written feedback into the actual text
2.5	26/12/16	R. Draft	Vasilis Megalooikonomou, Dimitris Vlachakis	Additions, comments, suggestions, answer to reviewers' comments
2.6	26/12/16	R. Draft	Athanase Benetos (INSERM)	General Review
2.7	27/12/16	R. Draft	Marina Kotsani, Athanase Benetos	Incorporation of all feedback, general review, minor corrections.
2.8	27/12/16	R. Draft	Vasilis Megalooikonomou	References' addition
2.9	27/12/16	Final	Marina Kotsani	Document finalisation
3.1	6/11/17	Revision Draft	Marina Kotsani	First approach to revision
3.2	9/11/17	R. Draft	Yannis Elloul	Additions, comments, suggestions, answer to reviewers' comments
3.3	9/11/17	R. Draft	Vasilis Megalooikonomou	Corrections to draft
3.4	9/11/17	R. Draft	Marina Kotsani	Incorporation of feedback, addition of references, paging
3.5	10/11/17	R. Draft	Eva Zacharaki	Additions, answer to reviewers' comments
3.6	10/11/17	R. Draft	Vasilis Megalooikonomou	Corrections to draft, General Review
3.7	10/11/17	R. Draft	Athanase Benetos	Corrections to draft, General Review
3.8	13/11/17	Final	Marina Kotsani	Document's details finalization

EXECUTIVE SUMMARY

The present report constitutes the deliverable D2.1- “Clinical study methodology” which aims at describing the operational procedures during the running of the protocol, standardize the series of the events, select the methods for the realisation of the comprehensive geriatric assessment and the rest of the clinical evaluations and measurements, consolidate the clinical interview’s battery, describe to some extend (that does not overlap with other deliverables) the sensors and technical material which will be used by the participants and define the general ethics and safety framework. All these are described in accordance to the original approved proposal.

The current deliverable is directly connected with "Task 2.1 Clinical study methodology and planning", one of the most important tasks of WP2, and it is expected to be utilised for the clarification and the standardization of the operational procedures of the FrailSafe study and to summarize a consensus for clinical strategies.

In the same time, this report is also a living document, with some of its aspects and descriptive procedures, mainly concerning the FrailSafe system’s technical material, susceptible to modifications according to the system’s own evolution, in accordance to the project’s objectives.

However it is out of the scope of the present deliverable to describe the end-product’s characteristics and the modalities of its use during the commercialization phase of the project.

The first and second part of the report summarizes the overall study design and early actions, mainly regarding the participants’ characteristics and recruitment. The third part of the report describes the measurements and tools to be used, while afterwards (in the fourth part), the time schedule and steps programmed for each group are described as a series of actions to be followed. The fifth part is dedicated in the presentation of the architecture of data analysis; in this part, the study’s outcomes are more clearly defined, the construction of Frailty Indices as frailty metrics are described, hypothesis are generated according to operational variables’ definition and the study’s objectives and an approach to the statistical analysis to be conducted is presented. Finally a reference to safety and ethical issues is done in the sixth part of the deliverable.

A list of annexes corresponding to the exact questionnaires to be delivered is presented in the document’s end, which, along with the tables throughout the text that refer to the various clinical assessment subsets, constitutes the whole battery of the questionnaires to be administered.

TRACK CHANGES

The present deliverable was modified for a second time according to the reviewers' comments, following the Review Meeting in Patras on September 28th and 29th 2017.

In Section 2.3 some details about the replacement strategy of the drop off participants have been given (page 20).

In Section 2.4 the issue of the frailty groups' ratio has been addressed (pages 21-22).

The way of managing the delays observed so far is treated in Section 2.6 (page 29-30).

Finally, in Section 5.2.2 details about proxy outcomes are provided (page 77-79).

DOCUMENT INFORMATION

Contract Number:	H2020-PHC–690140	**Acronym:**	FRAILSAFE
Full title	Sensing and predictive treatment of frailty and associated co-morbidities using advanced personalized models and advanced interventions		
Project URL	http://frailsafe-project.eu/		
EU Project officer	Mr. Jan Komarek		

Deliverable number:	2.1 revised	**Title:**	Clinical study methodology
Work package number:	2	**Title:**	Clinical studies, measurements, clinical analysis

Date of delivery	**Contractual**	**10/11/2017 (M23)**	**Actual**	13/11/2017
Status	Draft ☐		Final ☒	
Nature	Report ☒	Demonstrator ☐	Other ☐	
Dissemination Level	Public ☒	Consortium ☐		
Abstract (for dissemination)	This deliverable reports on the operational procedures during the running of the protocol, the time schedule, the methods for the realisation of the comprehensive geriatric assessment and the rest of the clinical evaluations and measurements, the clinical interview's battery, the sensors and technical material which will be used by the participants and the general ethics and safety framework. Revised according to reviewers' feedback.			
Keywords	Protocol description, operational procedures, timetable, time schedule, planning, groups, clinical assessment, questionnaires, frailty metrics, comprehensive geriatric assessment			

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List of abbreviations and acronyms

(*in alphabetic order*)

ADL	Activities of Daily Living
AIC	Akaike information criterion
ANS	Autonomic Nervous System
AR	Augmented reality
ARSG	Augmented reality serious games
BIC	Bayesian information criterion
BMI	Body Mass Index
BN	Bayesian Networks
BP	Blood Pressure
CGA	Comprehensive Geriatric Assessment
ClFI	Clinical Frailty Index
CoFI	Combined Frailty index
CSP	Central Systolic Pressure
DB	Deep Breathing
DBNs	Dynamic Belief Networks
DEXA	Dual energy X-ray absorptiometry
e-CRF	Electronic Case Report Form
eFI	Electronic Frailty Index
FS	FrailSafe
GDS	Geriatric Depression Scale
HR	Heart Rate
HRV	Heart Rate Variability
IADL	Instrumental Activities of Daily Living
ID	Identification
IMUs	Inertial Measurement Units
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
MO	Medical Objective
MRI	Magnetic Resonance Imaging

NLA	Natural Language Analysis
PWV	Pulse Wave velocity
QoL	Quality of life
TFI	Technical Frailty Index
UoP	University of Patras
VAS	Visual Analogue Scale
VE	Virtual Environment
VPM	Virtual Patient Model
VR	Virtual Reality
WWBS	Wearable WBan System

1. Introduction

FrailSafe project is a novel approach to a complex and under-understood medical, social and public health problem. The prevalence of frailty in a numerous and growing population group, older adults, as well as its implications in the person's health status and autonomy, naturally leads to the notion that understanding and managing this widespread condition is a priority for modern societies. Despite its importance, we still stand far from mastering the identification, early detection, effective management and prevention of frailty. One of the most important reasons for this is the lack of acute measurements and sensitive instruments able to identify frailty and pre-frailty conditions.

The FrailSafe project aspires to approach frailty in a global way, identify its most important components, quantify measurable parameters, construct cumulative metrics that will serve as biomarkers and apply this knowledge and expertise in the fields of management and prevention, in personal and even population basis.

In section 2 of this report the study methodology is presented. The first paragraph refers to the study's objectives and overall design, whereas the second, third, fourth and fifth paragraphs are devoted to the participant's characteristics, the sampling and recruitment procedure, the groups and the time schedule of the study respectively. The parameters, measurements and tools employed are described in section 3, divided in the clinical evaluation- comprehensive geriatric assessment, the data collection regarding social interaction and natural language analysis, blood sampling and complementary investigations and the operational procedures and technical equipment parts. Section 4 presents in the form of a timeline, the series of steps to be followed for each of the study groups. Section 5 refers to the architecture of data analysis. Section 6 approaches safety and ethics issues. Finally, section 7 contains the report's references, whereas section 8 consists of annexes corresponding to some of the study's clinical questionnaires.

2. Study methodology

2.1 Study's objectives and overall design

FrailSafe clinical study's main objectives are:

- To better understand frailty and its relation to co-morbidities

- To identify quantitative and qualitative measures of frailty (through advanced data mining approaches on multiparametric data) and use them to predict short and long-term outcome and risk of frailty
- To develop real life sensing and intervention platform offering physiological reserve and external challenges
- To provide a digital patient model of frailty sensitive to several dynamic parameters, including physiological, behavioural and contextual
- To create “prevent-frailty” evidence-based recommendations for the elderly; to strengthen the motor, cognitive, and other “anti-frailty” activities through the delivery of personalised treatment programmes, monitoring alerts, guidance and education
- To achieve all with a safe, unobtrusive and acceptable system for the ageing population while reducing the cost of health care systems.

The main objective of the FrailSafe study could be summarized in the investigation of the added value that brings the integrated FrailSafe system on the standard clinical approaches of frailty, in terms of earlier and more accurate detection and even prediction of its evolution.

FrailSafe study is an interventional, non-pharmacological, cohort study testing the efficacy of a series of novel instruments aiming to detect and quantify frailty. During its development (36 months), 510 older individuals living in the community will be enrolled and followed up in terms of their health conditions. During the primary phases of the study (M4-M30), intensive clinical studies will be performed aiming to provide sufficient data for the quantification of the FrailSafe computational models and augmented reality framework (ground the models and algorithms with experimental data, quantify and fine tune the intervention services). During the test and evaluation period (M31-M36) the clinical studies will focus on evaluating and validating FrailSafe developments.

The study’s interventions are at two different levels: a- application of the FrailSafe system in the majority of the participants (groups A, B, C) in order to monitor frailty-related parameters and, mostly b- an individualized interaction of a subgroup of participants (group C) with the FrailSafe system, through augmented reality serious games, recommendations using advanced human-computer interaction conversational agents (regarding lifestyle, daily activity, exercise, nutrition, etc) and personalized guidance in the form of consultation recommendations and assistance to its accomplishment.

The target population is adults older than 70 years. Although, for practical reasons, individuals with serious health conditions threatening the prognosis will be excluded from the study, the results anticipated will possibly benefit a wider range of older population. By studying a great variety of conditions and many of their combinations, abundant data will be collected and therefore, translation in many real life situations can be expected.

Various methods to detect and measure frailty will be employed, starting from the extended form of a classical clinical evaluation, namely the comprehensive geriatric assessment (CGA) and extending to the usage of novel high technology instruments, constituting the FrailSafe system.

The CGA will approach quantification of frailty by evaluating a person's medical history and prescription, cognitive and emotional status, autonomy, pain, balance and gait patterns, sensory system performance, nutritional status, living conditions, social life, leisure activities and quality of life self-perception. The quantification of these aspects of a person's global health condition will be done by using questionnaires and standardised scales, as well as cumulative indices, and this evaluation will be repeated throughout the study's duration.

On the other hand, the FrailSafe system attempts to depict a subject's frailty status in a more sophisticated and precise way. It consists of various sensors with the ability to record a large amount of data corresponding to several parameters like weight, body fat, blood pressure, pulse waves velocity, heart and respiratory rate, physical strength and activity, postural and movement information, localisation and cognitive performance. Most of the parameters' measurements will take place in real time circumstances in the person's natural environment, in the least invasive way possible. One of the originalities of the project is that the FrailSafe system will be developed and ameliorated during the study's evolution with the help of the preliminary results that will return to the engineers the participant's feedback and experience.

Using this large-scale data collection methodology, it will be possible to make comparisons between the clinical expression of different frailty levels and also between the performance of various measurements and tools to identify and even predict frailty.

Outcomes to be evaluated will be some hard and proxy clinically significant events, the evolution of frailty status of each individual (as measured by structured frailty indices) and the ability of each instrument to measure accurately frailty and its modifications and to predict frailty related outcomes. A secondary outcome (during the phase of parallel Evaluation and Control groups' testing) will be also to evaluate the possible difference in terms of evolution of frailty status between the individuals who received the FrailSafe system feedback and guidance and those who did not. Compliance rates and user satisfaction will be also tested. Shorter periods of monitoring will be compared with longer periods of monitoring to identify cost effective approaches.

By emerging the parameters and instruments the most efficient to detect, quantify and predict frailty, this project aims at constructing new and novel evaluation tools which will serve as frailty biomarkers of high accuracy and predictive value. The translation of these results in clinical practise could contribute to the organisation of strategies to prevent frailty and loss of autonomy both in individual and in population scale.

2.2 Participants' characteristics

The Clinical study will be performed in 3 Clinical Centers: University of Patras (UoP), Greece; INSERM-Nancy, France; and MATERIA- Nicosia, Cyprus. Each Center will recruit 170 individuals for the FrailSafe study. By this way a total of 510 community living subjects aged 70 years and older will be recruited. The inclusion and non-inclusion criteria are demonstrated in table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Age ≥70 years Informed consent provided
Exclusion criteria
Lack of wish to participate Consent withheld Inability to give consent because of incapacity Inability to walk Inability to speak Greek or French (see clinical centers) Diagnosis of clinically significant cognitive impairment or score less than 24 on the Mini–Mental State Examination Diagnosis of advanced malignancy, other terminal illness or an estimated life expectancy of less than 12 months Active psychiatric disorder based on medical records or clinical opinion at the time of recruitment, current substance users, or excessive alcohol drinkers.

The numerical threshold for "older age" has always been controversial, though most widely accepted was the age of 65 years, corresponding in the usual age of retirement. Still, nowadays "young old" individuals maintain a good general health condition and with the exception of special cases, frailty is most likely to be encountered in older age ranges. In the FrailSafe study, since we need to include people in non-frail, pre-frail, as well as frail conditions, it was decided that the age threshold will be that of 70 years.

In order to be able to comply better with the requirements of the study (usage of technical material, cooperation for the testing of novel equipment, need for participant's feedback and relatively long follow up period), subjects with highly debilitating conditions, such as inability to walk, presence of clinically significant cognitive impairment, or active psychiatric

disorder will be excluded from the study. Similarly, subjects with serious medical conditions that convey a guarded prognosis (estimated life expectancy of less than 12 months) will be excluded as well.

2.3 Groups

All participants will be given a unique number by the time they are allocated in four groups (table 2), with the addition of the code number of each centre in front: (1 for Patras, 2 for Cyprus and 3 for Nancy). For each centre, participants with numbers 001 to 080 will belong to the Start Up Group (A), the 40 following will belong to the Main Group (B), the 25 following afterwards will belong to the Evaluation Group (C) and the last 25 to the Control Group (D). The Evaluation Group (C) will be further divided in two parts: participants with numbers 121-140 will belong to the "standard" Evaluation Group; while those with numbers 141-145 will belong to the Long Term Evaluation Group, with an augmented intensity of following up.

Table 2. Participants' ID numbers

Group	Serial Number
A- Start Up	001-080
B- Main	081-120
C- Evaluation	121-145
Ci- Standard Evaluation	121-140
Cii- Long term Evaluation	141-145
D- Control	146-170
With the prefix of the centre number	1 for Patras, Greece 2 for Nicosia, Cyprus 3 for Nancy, France

In case of exclusion or premature withdrawal of a participant, (s)he has been replaced by a new subject, to whom a new unique ID number has been given. The substitute subjects were given the number of the individual they have replaced with the addition of 500. For example, if the participant number 1094 withdrew from the study (subject number 94 from the first recruitment centre), the subject that replaced him/her will take the number 1594

(=1094+500). For subject number 3164 who withdrew (participant number 164 from the third recruitment centre), the subject replacing him/her will take the number 3664 (=3164+500). However, participants' replacements took place only until M19. Any subject that dropped off after July 2017, has not been and will not be replaced due to lack of time for catching up with the minimum follow up time period required (M19 represents the middle timeline of the project).

The number of the participants allocated in each group is already agreed in the original proposal and corresponds mostly to issues of availability of material and workforce in the context of actual financial potential and less to pure mathematical calculations, due to the originality of the project and the absence of a previous reference to consider for sample size calculations.

2.4 Sampling, recruitment procedure and randomization

The method of sampling from the general population will be the convenient method, in order to create a pool of candidate participants. Although it might not be the most unbiased method of recruitment, it is the most suitable for the present study mainly because our participants are actually volunteers. We addressed to them, in their natural environment (community settings, their own home) in order to ask them to voluntarily participate in the FrailSafe project.

The recruitment strategy will be organized by each one of the 3 centres individually. Main procedures that were followed are collaborations with older people's associations and public events in order to inform people about the importance of intervening on frailty and the objectives of FrailSafe study. More specifically, we approached medical institutions and rehabilitation centers, public organizations and local societies/associations, home care services, older people's and relatives' focus groups and individuals occupied with health care provision. In parallel, a communication policy by advertising in the mass media was attempted (local television channels, newspapers and websites), with very satisfying results.

The aforementioned strategy aims not only at attracting interested individuals eligible for the study, but also at spreading the word in people who are not necessarily eligible, but who could mobilize their friends and relatives and inform their personal or professional environment.

Inevitably, a certain degree of motivation bias is inherited in this project, and cannot be fully excluded. Potential participants in all centers were asked to participate after explaining the study procedures in details. Individuals who were not motivated declined to consent. To overcome, as much as possible, this issue was stressed the future benefits of the study, as well as the activities and interaction during the study that may spice up the daily routine.

Despite the overall common procedures, different enrollment strategies were somehow proved to be more effective in each clinical center. For instance, INSERM (France) mainly carried out public targeted meetings inviting older people to participate, whereas in Patras (Greece) the local Geriatric and Gerontology Society mainly invited its members to participate, and similarly MATERIA (Cyprus). Therefore in the whole, the study sample was not made only by self-volunteered participants.

By this extrovert approach a pool of interested individuals is created and eligible participants (subjects who seemingly fulfil the inclusion and non-inclusion criteria) are been called by telephone to make a first appointment.

During this first meeting the individual are thoroughly informed (information letter and supplementary oral information), questions are answered and, in case of agreement, an informed consent is signed. Data regarding social interaction and natural language analysis is collected. A first clinical evaluation follows (part of the clinical evaluation battery-section 3.1) in order to investigate the Fried's criteria of frailty, comorbidities and cognitive status (tables 6, 9 and 13). This information is necessary for:

- The classification into frailty categories. The participants will be classified in three groups according to their frailty status assessed by the criteria of Fried's frailty index (1) (table 9). Individuals with 3 or more criteria will be allocated in the frailty category, those with 1-2 criteria will be characterized as pre-frail, while those with no frailty criterion will be characterized non frail.
- Identification of leader co-morbidities: history of stroke, mild cognitive impairment (MCI), osteoarthritis for men and osteoporosis for women.
- The verification of inclusion and non-inclusion criteria. In case of exclusion, replacement of the participant with another subject will take place. For this reason the pool of our candidate participants should be considerably larger than the number of subjects that actually need to be recruited.

The proportion of subgroups ("non-frails", "pre-frails", and "frails") according to the Fried's frailty criteria was changed from the initial 2:1:1, i.e. non-frail (50%): pre-frail (25%): and frail (25%), to 1.5 : 1.5 : 1 for groups A and B added up together.
This proportion is more favorable and exploitable due to the following reasons:

- We considered the risk that there will not be enough users to achieve project's objectives related to frailty itself as pointed out by the experts in the 1st review of Frailsafe (see recommendations FR1 and FR2). The project focuses mostly on non-frail and pre-frail people since the frail group does not offer much in monitoring the transition between states.
- Non-frail and mostly pre-frail individuals are more likely to benefit from interventions in terms of prevention of evolution of their frailty status (MO3), than the already frail ones that are less likely to regress to a previous frailty status.
- Especially the pre-frail individuals, that outweigh other categories in our population, are those who are traditionally considered to benefit more from potential interventions and thus are generally the target of the standard CGA (ie, excluding patients who are either too well or are too sick to derive benefit) (MO4) (1). If the

FrailSafe system is to be tested for its added value on the standard CGA (main medical objective), pre-frail individuals should be the dominant target group.

- Our study focuses on prevention (MO6), therefore, a smaller number of already frail people should be allowed. However, they should also exist in our study population in order to enable us to make comparisons and draw conclusions.
- From the very first analysis that has been performed and presented in D2.6 Behavioral management, we observe that the pre-frail category almost constantly scores in between the performances of the non-frail and the frail group in all tests and parameters. This emphasizes the fact that they constitute a dynamic intermediate category with the potential to approach either the one or the other extreme (MO5). Thus, the results of potential interventions could be measurable and could contribute to the prevention of category shifting towards frailty.
- Under the prism of a potential exploitation of the FrailSafe end product in the future, individuals, health care professionals, insurance companies and health policy makers could be more interested to apply the integrated FrailSafe system in people that are already threatened by a devastating health condition such as frailty (ie the pre-frails), rather than devoting resources in a totally healthy population, who might not be eligible for reimbursable health interventions. Therefore this frailty category is considered to be of great interest for the FrailSafe project (MO7).

The above listed proportions are calculated on the total of participants, in the sum from all three centers, so different percentages may be present within groups from Cyprus, Greece and France. However, the same criteria (Fried's)(2) (table 9) will be applied in all clinical centers.

This stratification of frailty according to Fried's criteria will not be used in the analysis of data. The study population will be considered as a whole, from which new frailty metrics will be identified using both hard and proxy outcomes; the latter will be based on the change of clinical and FrailSafe parameters.

The sample in this study should ideally be randomly selected from the general population in those aged ≥70 years. This would require a larger number of participants and a larger number of study workforce, as well as equipment, in order to include individuals with the right case mix of frailty levels and a representative number of comorbidities. Undoubtedly, such a design would have been preferred and would have provided strong and reliable clinical results. However, current financial resources in this Horizon 2020 call, which are split among technological development and clinical evaluation, were not sufficient for this type of methodology.

It is understandable that transition among the groups as defined by Fried's criteria might not be easily observed with the current study design, as number of participants, time span and number of simultaneous FrailSafe assessments are limited. On the other hand, functional changes or proxy outcomes expressing loss of functional reserve is likely to be detected when the study group is examined as a whole. The choice of the current clinical study methodology was a compromise between an ideal approach and a more practical solution, though hampered by numerous limitations.

In addition, in each of the three frailty status, at least 7 have prior stroke, 7 MCI (Mild Cognitive Impairment), 7 either osteoporosis for women or osteoarthritis for men and 7 nothing of the mentioned above. There is no particular concern in which group they will

belong. If this will not be achieved by randomization, the investigator, who will be in charge to overall monitor randomization, will intervene to further randomly stratify cases to obtain this pre-specified study objective.

The sample was recruited after specifying lower age limits and certain comorbidities. The intention which was described and accepted in the initial proposal, was to include certain key comorbidities, which are in a relatively low prevalence in elderly population. Otherwise, these comorbidities would have been under representative in our small sample, and their effect on frailty process might have been lost. These comorbidities, among many others equally important, may accelerate the frailty process; they may also influence the scoring of frailty according to Fried's criteria. For instance a previous stroke or the presence of osteoarthritis may slow down the speed of walking altering the frailty score, whilst at the same time would not contribute to a functional worsening in time. Mild cognitive impairment may have an opposite effect, as it does not directly modify the Fried frailty score, but may strongly influence the loss of functional reserve.
During clinical evaluation, together with the pre-specified comorbidities, up to twenty seven other possible medical conditions/comorbidities are also recorded. Thus, the analysis of data regarding comorbidities will not be carried out exclusively around the pre-specified ones. The absolute number of accumulated comorbidities, the absolute number of the most prevalent comorbidities, and a choice of the most prevalent comorbidities will be explored as independent or confounding factors to the frailty process. An effect on functional change may be shown by adding or subtracting groups of individuals with common comorbidity/ies.

Randomization will take place for groups C (Evaluation) and D (Control)(section 2.4) in a later study period (M10-M30). The randomization has proven to be practically difficult for groups A (Start Up) and B (Main), due to the almost coincidence of their recruitment in the beginning of the study and the large number of participants they required. As the dissemination campaign advanced progressively, it turned out to be difficult to have in our availability, since the very initial phase of the clinical study, an even larger pool of participants in order to strictly randomise them. Instead, we included in the first group the first 80 subjects that expressed their interest for participation in each centre, followed by the 40 consequent ones, who were finally allocated to group B. We estimate that since in the present phase of the clinical study the objective is to validate the FrailSafe system and to test its detection sensitivity and not to compare interventions (as will be during the groups C and D parallel evaluations), and since we have no reason to believe that the subjects who were recruited during the first dissemination activities differ significantly from those who were informed about the study in a later stage of the recruitment campaign, the consortium believes that this lack of randomization in the very first phase of the study will not affect results, since comparison between groups will take place later between group C (evaluation) and D (control).

In a later period during the study (M20-M30), recruitment campaigns will start again in order to create the pool of eligible subjects from which participants for group C and D will be randomly selected.

In addition, the participants of the evaluation group C will be further randomized (1:1) into two categories either to receive a tailored set of lifestyle, nutrition and exercise recommendations (predetermined recommendation and "intervention" proposals based on the monitoring performed using the Frailsafe system) or to receive general life style recommendations (standard care). The technical personnel responsible for the extraction and analysis of data will be blind on randomization procedure.

2.5 Time schedule

All individuals with numbers 1-146 (groups A to C) will undergo the main evaluations, assessments and interventions and a blood sampling in the beginning of the study. Differences among groups concern the timing and the frequency of these interventions (figure 1). The last 25 participants (control group) will not test the FrailSafe system, but will receive two clinical evaluations, one blood taking and one telephone follow up interview. For all participants, data regarding social interaction and natural language analysis will be collected by their entry to the study. Data collection of written text will be repeated in the context of each clinical evaluation session.

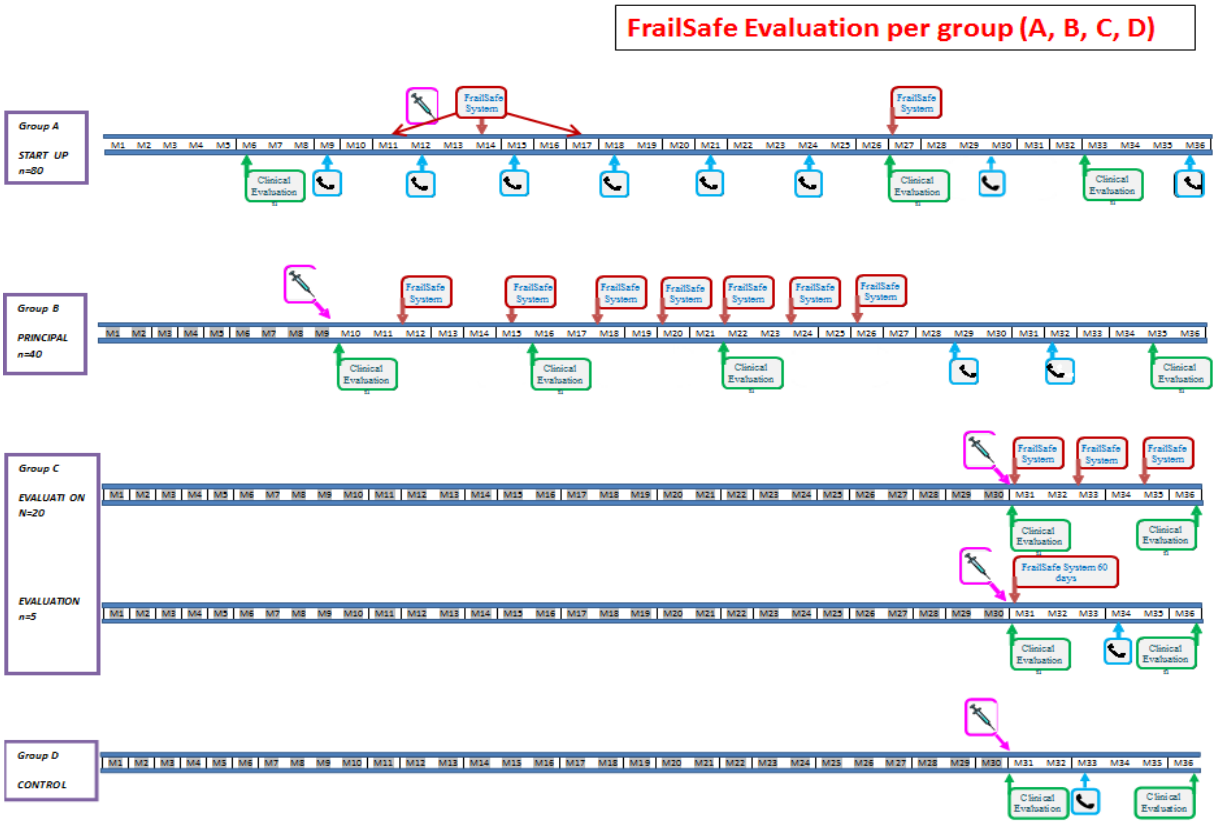


Figure 1. FrailSafe study's time schedule per group and per center

In each clinical center the procedures followed are:

Eighty participants of group A were supposed to undergo a clinical evaluation, a blood sampling and a FrailSafe system instauration at the time of their recruitment (≥M6). However, the FrailSafe home visit, along with the blood drawing which accompanies it, was not possible to be done on time for all participants of group A. The reasons for this, along with a proposed mitigation strategy are described below (section 2.6). The second clinical evaluation session and FrailSafe system utilization is scheduled for M26 and a last clinical evaluation will take place in M33. Meanwhile, in 3 months intervals, there is the telephone follow up questionnaire up until M36, unless it coincides with a clinical evaluation or a FrailSafe home visit session, where it will be administered in person and not by telephone. A second blood sampling will take place in M27 only for a subgroup of participants in the clinical center of Patras' University.

The participants of group B (40 subjects) started in M10 by the clinical evaluation session. Similarly as in group A, and mainly because of the delay in this first group, the first FrailSafe system installation for group B, along with the blood taking that accompanies it, is not yet completed. The proposed mitigation strategy is described below (section 2.6). In this group the FrailSafe system application will be more intensive, every two or three (only for the first sessions) months, from M12 to M27, for a total of 7 times. The second and third clinical evaluation sessions will take place in M16 and M22 respectively. Finally, a last clinical evaluation session with take place in M35. Telephone follow up assessments will be done every 3 months' time from M26 to M36, but the follow up questionnaire will be administered in person in every FrailSafe home visit also from M12 to M22, during the corresponding appointments. In practice, group B due to its frequent FrailSafe home visits will receive no more than 2 follow up phone calls (M29 and M32). A second blood sampling will take place in M25 only for a subgroup of participants in the clinical center of Patras' University.

The group C will be the group to test the FrailSafe system in its integrity as it will be developed by the interactions and adaptations from the previous groups' experience. Starting in M31 the triplet clinical evaluation, blood sampling and FrailSafe system will be applied. Twenty of the participants in this group will have the FrailSafe system for 5 days (as used by the other groups also), 3 times in total with 2 months' intervals (M31 to M35). On the other hand, five individuals of group C will be asked to carry the FrailSafe system for 60 days in continuation. At the end of the FrailSafe system testing, a satisfaction interview will be conducted to each group C individual. All group C participants will receive a second clinical evaluation in the end of the study (M36) and a follow up questionnaire in M33 for the first arm of group C (during the second FrailSafe system home visit) and in M34 for the second arm of group C in M34 by telephone call. A second blood sampling will take place in M35 only for a subgroup of participants in the clinical center of Patras' University.

Finally the group D (control group) will receive no application of the FrailSafe system. A blood sampling will take place in the recruitment (M31), together with a clinical evaluation

session. The latter will be repeated once more at the end (M36). One telephone follow up will take place in M33.

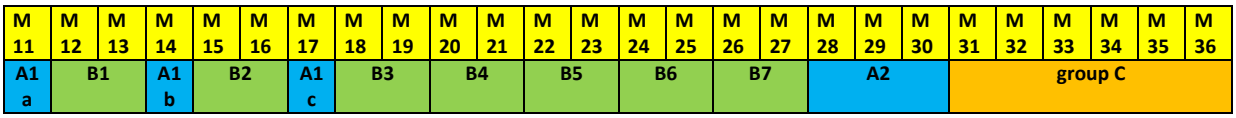
In case of premature exit from the study of an individual due to consent withdrawal, death or occurrence of another condition rendering the participation impossible and provided that less than the 50% of the assessments scheduled were accomplished, each departing participant will be replaced by a new one. For the latter, the time schedule of the follow up planned will be shifted forward to the time line of the departing participant after starting from the basic beginning's triplet: clinical evaluation, blood sampling, FrailSafe system. In case the replacing subject also drops out of the study, no further replacement is scheduled for technical reasons.

The time schedule presented above remains a framework that it is possibly subject to adjustments according to the availability of each individual. This study aims to be the least invasive possible in terms of participants' regular life planning and activities. Under this perspective, reasonable deviations of the scale of ±1 month should be considered acceptable.

2.6 Deviations from the original plan and proposed mitigation actions

Already since the beginning of the study, due to delays in obtaining the Ethical Committees' approval in Nancy (France) and to limited availability of the FrailSafe system devices, there was a certain delay that affected the starting of mainly group A and partially of group B.

We have elaborated a proposed mitigation plan of a modified timetable for FrailSafe home visits in order to catch up with "lost" FS evaluations in group A, schematically depicted as following:



Legend:

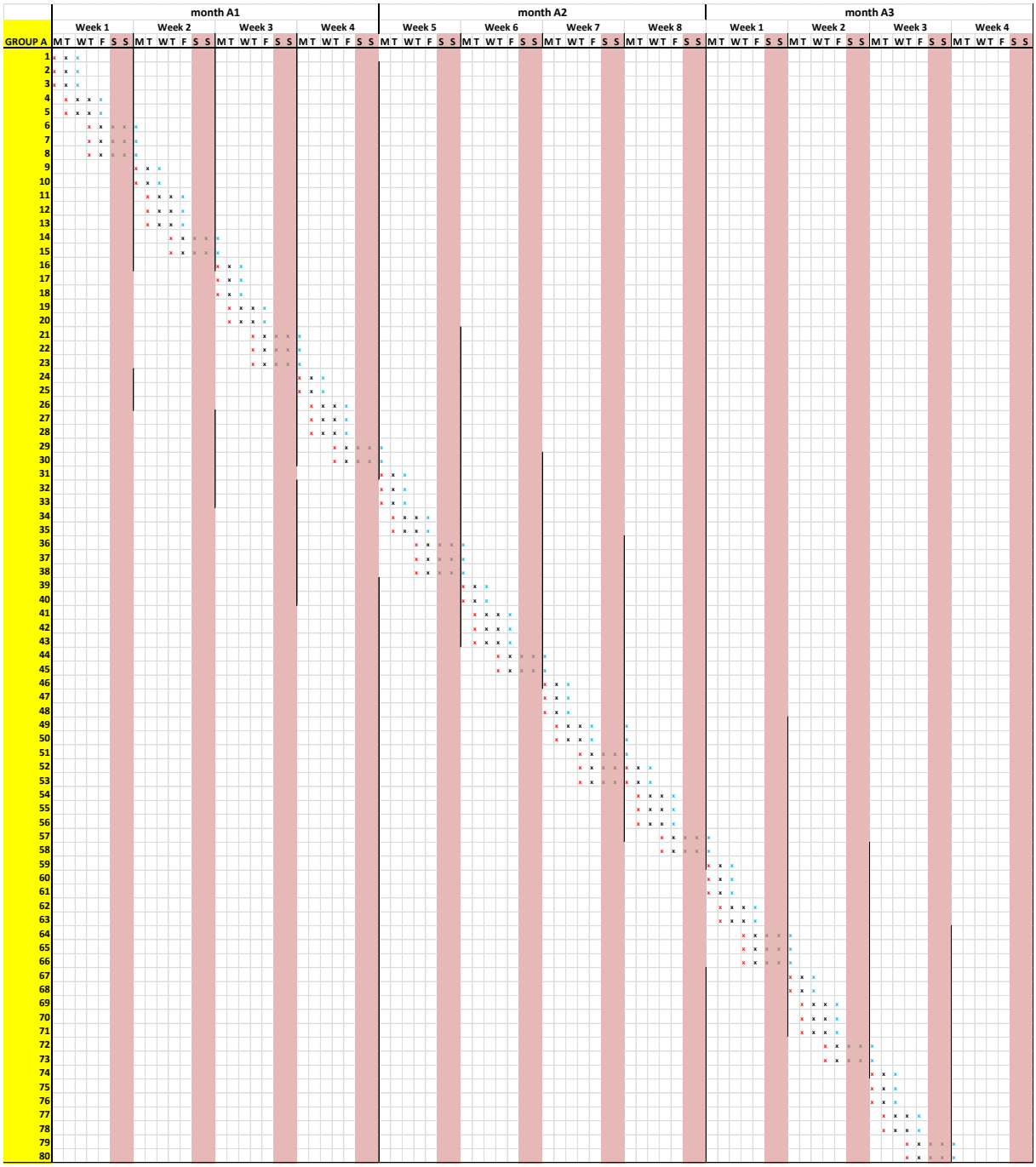
A1a	M11	first cycle first part 1-27(one month)
A1b	M14	first cycle second part 28-52(one month)
A1c	M17	first cycle third part 53-80(one month)
A2	M28-30	second cycle 1-80 (three months)
B1	M12-13	first cycle 81-120
B2	M15-16	second cycle 81-120
B3	M18-19	third cycle 81-120
B4	M20-21	forth cycle 81-120
B5	M22-23	fifth cycle 81-120
B6	M24-25	sixth cycle 81-120
B7	M26-27	seventh cycle 81-120

Figure 2. Mitigation action proposed for the FrailSafe system sessions

More analytically the plan proposes:

- The split in three of group A's first cycle of FrailSafe session and its interference between the 1st-3rd sessions of group B (M11,M14, M17)
- The decrease of the duration of FS session for group A (3-5 days instead of 5)*
- The reduction for group B of the total number of FrailSafe sessions' cycles in 7 (instead of 9 initially scheduled)
- No change in the conduction of the study for groups C and D (M31 and after).

*this proposal about the duration derives from the need to do all 80 first FrailSafe sessions per center in the shortest delay possible in order not to disturb too much the continuation of the study with the recruitment of group B. Taking into account that no more than five FrailSafe sessions can run simultaneously because of material and personnel availability reasons, the shortest time frame possible to make 80 FrailSafe home sessions is almost 3 months, as illustrated in the following schema:



Legend:

x visit for installation of FS material

x "on call"=possible visit if problem

x visit of retrieval of FS material

weekend

Figure 3. Schema illustrating the whole group A's first FrailSafe session in terms of time (80 subjects per center in less than 3 months' time)

We propose the splitting of group A's FrailSafe sessions and their distribution in between the sessions of group B.

The alternative of having all 80 group A's FrailSafe sessions in 3 consecutive months is not considered preferable because it will delay the FrailSafe sessions of group B's by the same amount of time (3 months), resulting in further protocol deviations for group B also.
We wish to preserve the integrity of the initial protocol for group B in terms of:
-the synchronization of the first FrailSafe system sessions with the corresponding clinical evaluations
-and the duration of the FrailSafe sessions, which will remain 5 days as originally predicted.
The time required for accomplishing each FrailSafe session cycle in 40 participants per center is 2 months as depicted in the following schema:

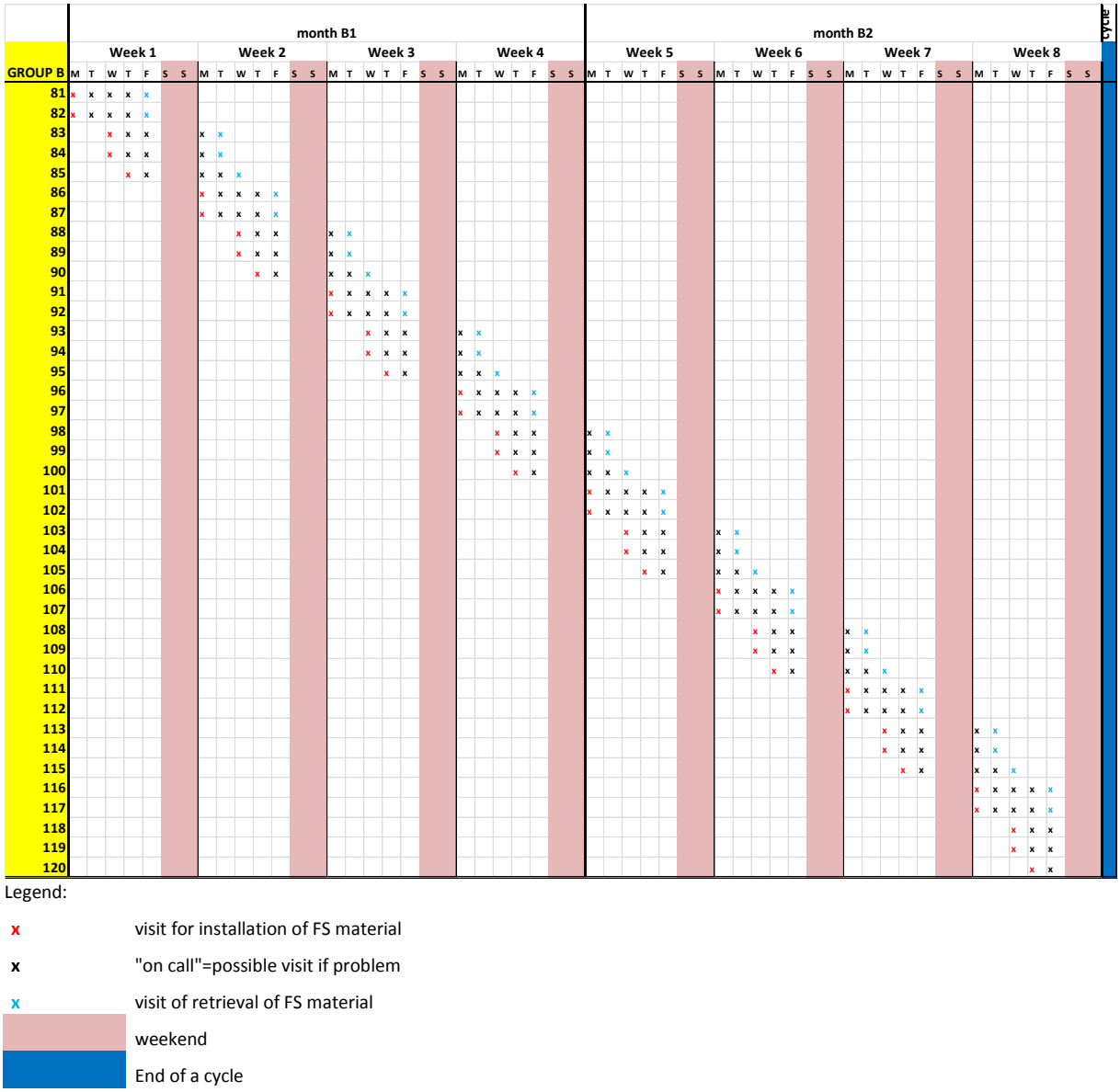


Figure 4. Schema illustrating the first cycle of group B's first FrailSafe session in terms of time (40 subjects per center in 2 months' time). The same pattern should be repeated another 6 times completing the 7 FrailSafe sessions proposed by the mitigation plan.

By the time this revised version is written (beginning of M23), there has been a delay of approximately 3 months' time for group B FrailSafe sessions. The consortium's intention is to

respect the protocol at its mitigated version so that the data analysis is the most robust possible. We consider the aforementioned plan as a competent one, since it has been effective in catching up with at least part of the initial delay (e.g.,. Nancy's clinical centre managed to synchronize its actions with the other centres), whereas its current delay is mostly the result of occasional difficulties and particular circumstances (e.g., reduced availability of several participants during summer time, extra time required for replacing individuals that dropped off, etc). Therefore, and despite the current delay, we consider that this schedule should continue to be followed by clinical centres.

However, the re-evaluation of the status of the clinical study, the alternatives offered at the time and the possibility of a request for a study prolongation will be reconsidered in M27, which is the month that the FrailSafe home sessions are supposed to be completed. Based on the number of sessions achieved by that time, and mostly on the results of the data analysis that will be performed, a more concrete and informed decision about the need and the required duration of a prolongation period will be taken by the consortium and proposed to the Commission. We consider M27 more appropriate than the present moment, since MO3 (=use quantitative and qualitative measures to predict short and long-term outcomes) will be better served in an analysis performed later on and thus a more precise estimation of the prolongation needed can be done at the time. Potential changes detected later on in the timeline of the project also serve better MO5 (provide a model sensitive to change…) and thus the postpone of a mitigation decision will work in favour of the right decision to take, because of the availability of more data. Acceptability issues, mainly addressed by MO7 (achieve all with a safe and acceptable to older people system) should be a consideration before immediately rushing to the prolongation option, that could induce a type of inconvenience in older people's routine.

3. Parameters, measurements and tools

3.1 Clinical evaluation-Comprehensive Geriatric Assessment

The clinical evaluation session employs the classical means that are routinely used in clinical practice up until now in order to detect and quantify frailty, globally evaluate the older patient's health and organise strategies of management. The comprehensive geriatric assessment is a laborious and generally time consuming complex procedure, initially analytic and eventually synthetic, which requires skills and expertise. To facilitate, speed up and broaden the applicability of CGA, many tools have be developed and proposed for each of its aspects, mostly in the form of detection or evaluation short scales.

For our clinical assessment sessions we have chosen widely recognized and used scales and questionnaires and also some structured questions that correspond to the needs for data collection of this study. Moreover, we employ some metrics of anthropometric and cardiovascular parameters (height, weight, body mass index, body fat, arterial blood pressure, pulse wave velocity and central systolic pressure), using adapted instruments. The battery of questions and the clinical measurements that are used will remain mostly the same all throughout the study's duration, with the exception of some data that are going to be collected only once in the beginning and potential need for additional information collection if this is required during the study's development and adaptation process.

The clinical evaluation session will be divided in assessment subsets, corresponding at different aspects of CGA (table 3).

Table 3. Clinical assessment's subsets	Tools to be employed
1. Identification data	Questions
2. Generalities: demographics, leisure, social life/communication assessment	Questions
3. Medical history, comorbidities, medication list	Questions, self-reporting, drug prescriptions, medical records when available
4. Clinical examination and instrumental measurements	Pulse palpation, measure tape, FORA scale, electronic tension meter, mobilograph
5. Balance and gait evaluation	Stopwatch, meter, IMUs
6. Fried's criteria of frailty assessment: allocation into frailty categories	Questions, dynamometer
7. Sensory system evaluation: vision, hearing	Questions and clinician's estimation
8. Nutritional Assessment	MNA short and extended form
9. Activities of Daily Living	Katz Index of Independence of ADL, Lawton IADL scale
10. Cognitive, mood and sleep evaluation	MMSE, MoCA, questions, GDS-15items
11. Self-evaluation scales	Questions and VAS

The very first clinical evaluation session is divided in two parts. In the first part identification data is recorded (assessment subset 1,2-table 4,5), the Fried's criteria of frailty are examined

(assessment subset 6-table 9), the comorbidities are recorded (assessment subset 3-table 6), a short cognitive assessment takes place (assessment subset 10-table 13). This very first evaluation allows the verification of inclusion and exclusion criteria (table 1) and the classification to frailty levels and comorbidities' status. If a seemingly eligible in the beginning subject turns out, by this first part of the clinical evaluation, to have for example a MMSE<24, an active psychiatric disorder, an alcohol or drug abuse, or a poor prognosis condition, this subject will exit the study and will be replaced by another one. In other case, after the confirmation of the subject's eligibility to the study, the randomization and the allocation to groups, the rest of the clinical evaluation takes place (assessment subset 4, 5, 7, 8, 9, 11).

After this first clinical evaluation session, the rest that follows will take place as a single battery at the same time.

Together with the clinical assessment subsets, data regarding social interaction and natural language analysis are collected.

3.1.1 Assessment subset 1: Identification data

This section includes:

- the participant's ID number: a four digit number where the first number corresponds to the center (1 for Patras, 2 for Nicosia and 3 for Nancy) and the three following to the number given to each participant when they enter the study. This ID number is unique, and serves to identify and spot a participant all throughout the study.
- the group allocation: according to the order of entering the study and the ID numbers, individuals are allocated in groups START UP, MAIN, EVALUATION and CONTROL, as described in section 2.3.
- the date of entry in the study: corresponds to the date of informed consent signature
- the subject's initials: to avoid personal identity unmasking in the e-CRF only the first two letters of the participants' first and last name are noted.
- year of birth: since only rough chronological age serves equally well the purposes of the study, no exact date are noted in order to avoid the risk of personal identity unmasking.
- sex

The identification data, since they remain unchanged in time, are collected only once during the first clinical evaluation appointment and from that point on only the ID number will be used to identify each subject. Each center holds the responsibility to keep separate and secured archives of more extended identification data of each participant, including their contact details. Table 4, summarizes this sub questionnaire.

Table 4. IDENTIFICATION DATA

Participant ID number	
Group	START/ MAIN / EVALUATION/ CONTROL
Date of entry in the study	*Corresponds to the date of the consent signature*
Name initials	*First two letters of First and Last name*
Year of birth	
Sex	M/F

3.1.2 Assessment subset 2: Generalities and demographics

This section serves for the collection of some demographic data and also as a means to establish the first contact with the participant and smoothly introduce the whole battery. It includes:

- information about the living conditions: mostly to investigate the level of isolation and the need of external help
- family status
- profession: as an indirect index of socio-economic status
- education: as an indirect index of socio-economic status and helpful co-variable to interpret some tests
- leisure activities and
- social life/communication: as indices of social activity, social surroundings and modern means of communication usage.

Obviously, the items referring to education and profession are filled in only once during the first clinical evaluation appointment. The rest of the information will be collected repeatedly. Table 5 summarizes this sub questionnaire.

Table 5. GENERALITIES AND DEMOGRAPHICS

Living conditions	*Choose all that apply:* 1.lives alone 2.live with spouse/companion 3.live with another/other relative(s) 4.family/close friends nearby 5.Presence of regular help (professional or family)
Family status	*Choose one answer:* 1.Single 2.Married or in a relationship 3.Divorced 4.Widow
Profession	*Choose one answer:* 1-Housewife 2-Agriculture Workers (farmer, breeder etc) 3-Workers (manual labor workers, factory workers) 4-Craftsmens, Merchants (enterprising, businessmen etc..) 5-Intermediary professions (ex. sailors? seamen? drivers? Free professionals?) 6-Employees, Officers, Clerks…. 7-Executive employees and intellectual professions (teachers, professors, tutors, physicians, engineers, lawyers etc)
Education	Number of educational years *Write down the number. Values of 0 also acceptable*
Leisure activities	How many times do you go out of your house per week? *Write down the number. Values of 0 or decimals also acceptable. "I don't know" option also provided* Are you member to a club or an association? Yes/No

Social life/ communication	How many times per week do you exchange visits with somebody (either you visit them or vice versa)? *Write down the number. Values with decimals also acceptable. "I don't know" option also provided* How many times per week do you receive or give telephone calls (or other means of distance communication) with someone close? *Write down the number. Values with decimals also acceptable. "I don't know" option also provided* What is the mean time you spend speaking at the phone per week (in minutes)? *Write down the number. Values with decimals also acceptable. "I don't know" option also provided* What is the mean time you spend on videoconference per week (in minutes) either on your own of assisted by someone else? *Write down the number. Values with decimals also acceptable. "I don't know" option also provided* What is the mean number of text messages you send per week either on your own or assisted by someone else? *Write down the number. Values with decimals also acceptable. "I don't know" option also provided*

3.1.3 Assessment subset 3: Medical history, comorbidities, medication list

This session compiles the medical history of the patient, mostly as it is reported by him or herself and extracted from the available medical records. Of course, this system bears some risks as far as the validity of the available data is concerned, but it is a methodology widely employed in large studies which do not aim primarily in the detailed study of each and every one of the corresponding co-morbidities. The focus of the present study is frailty and therefore there is no need in a thorough analysis with all diagnostic means for other pathologies.

In case of a serious medical condition such as an active psychiatric disorder, an advanced malignancy or other terminal illness of an estimated life expectancy of less than 12 months

or substance abuse comes out from the history taking, the subject are excluded from the study. The data to be collected, as well as its rational, consist of:

- Identification of an existing pathology from a pre-given list of common medical conditions with importance to older adults, based on self-reporting and available medical records' review (annex 1).
- Estimation by the physician of the effect of each of the comorbidities in the individual's functional status. This information provides us with an insight of the importance of each comorbidity and therefore its contribution to frailty. By this way the list of comorbidities obtains more than a catalogue value and reveals a short of ranking of their importance for frailty (annex 1).
- Lead comorbidity identification, according to the three comorbidities that were determined as important by the study's initial protocol: prior stroke history, mild cognitive impairment and osteoarthritis for men and osteoporosis for women (annex 2).
- Medication list: active substances and daily administration frequency will be recorded. Centralization of this information will allow to further prescription analysis and categorization of drugs takes according to the British National Formulary model. Polymedication is considered a major factor and index of frailty (3), while the frequency of daily drug taken is an index of burden in the everyday life of an individual and at the same time a potential source of medication errors (annex 3).
- Hospitalizations: which are considered an outcome unfavorable for older adults as they threaten autonomy (4) and in the same time frailty affects the outcomes of a hospitalization (5).
- Falls history: major geriatric syndrome closely related to frailty (6)
- Fractures history, date and localization. Fractures are a major complication of falls and negatively affect functional status.
- Physical activity is considered a major preventive measure against frailty, and at the same time its restriction constitutes criterion of frailty (7), (8), (2).
- Smoking status and
- Alcohol use: is of interest as habits significantly affecting health status. Moreover, the notion of excessive alcohol use is an exclusion criterion for the study. Alcohol use is quantified according to recommended use of no more than 3-4 alcohol units for men (3 for our study) and no more than 2-3 units for women (2 for our study). The alcohol units' equivalences that are going to be consulted are illustrated in annex 4 (9).

Table 6 summarizes this sub questionnaire.

Table 6. MEDICAL HISTORY, COMMORBIDITIES, MEDICATION LIST

Medical and Surgical conditions	*Comorbidities as self-reported by the participants and/or revealed by their medication list and/or medical records. (Annex 1)* *Check all that apply* ▪ ARTERIAL HYPERTENSION yes/no ▪ DYSLIPIDEMIA yes/no ▪ DIABETES MELLITUS yes/no ▪ ISCHEMIC HEART DISEASE yes/no ▪ CHRONIC ATRIAL FIBRILLATION/PAROXYSMAL AF OR OTHER ARRYTHMIA yes/no ▪ HEART INSUFFICIENCY yes/no ▪ STROKE OR TIA yes/no ▪ CHRONIC RENAL DISEASE yes/no ▪ CANCER yes/no ▪ RESPIRATORY DISEASE yes/no ▪ IMPAIRED COGNITIVE FUNCTION yes/no ▪ PARKINSON'S DISEASE yes/no ▪ EPILEPSY yes/no ▪ DEPRESSIVE MOOD yes/no ▪ ANXIETY AND/OR SLEEP PROBLEM yes/no ▪ URINARY INCONTINENCE yes/no ▪ PROSTATE PATHOLOGY yes/no ▪ ANEMIA yes/no ▪ JOINT PAIN- MUSCULOSCELETAL COMPLAINTS/DISEASES yes/no ▪ OSTEOPOROSIS yes/no ▪ CONSTIPATION AND OTHER INTESTINAL PATHOLOGY yes/no ▪ DYSPEPSY yes/no ▪ THYROID GLAND PATHOLOGY yes/no ▪ EYE DISEASES yes/no ▪ HEARING PROBLEMS yes/no ▪ DIZZINESS AND/OR VERTIGO yes/no ▪ LOWER LIMP TRAUMA OR OPERATION WITH RESIDUAL SIGNES yes/no ▪ Others (ICD-10 coding) yes/no
Estimation of the effect of each comorbidity in the individual's function	Do you think that each of the present conditions has a significant impact in the individual's functional capacity? yes/no

Lead co-morbidity among those with special interest for the study	Which is the most important lead co-morbidity *(Annex 2):* *One answer possible* • Prior stroke • MCI • Osteoporosis if woman /Osteoarthritis if man • None of the above • No comorbidity at all
Medication	The whole medication list *(Annex 3)* *(drugs over-the-counter and drug frequently- even not daily- used included)* Frequency of drug administration per day How many times a day (s)he takes each distinct drug
Hospitalization	Number of hospitalizations in the last year *"I don't know" option also provided* Number of hospitalizations in the last year and three years? *"I don't know" option also provided*
Falls	Number of falls in the last year *"I don't know" option also provided*
Fractures	Number of fractures during the last 3 years *"I don't know" option also provided* Number of fractures in lifetime *"I don't know" option also provided*

	Fractures' anatomic localization. *Click all that apply:* o upper limps o hip-pelvis o vertebral o other o multiple factures *"I don't know" option also provided* How many months before the study did your last fracture occur? *"I don't know" option also provided*
Physical Activity	Do you have regular physical activities (walking gardening, others). *One choice* 1. -No 2. -<2h per week 3. -2-5 h per week 4. - >5 h per week
Smoking status	1. Never smoked 2. Past smoker (stopped at least 6 months) 3. Current smoker
Alcohol use	Number of alcohol units' equivalences consumption per week *(Annex4).* *Values of zero or decimals also accepted*

3.1.4 Assessment subset 4: Clinical examination and instrumental measurements

This session will include mostly the instrumental part of the clinical evaluation.

- Arrhythmia detection by pulse palpation by a physician. The interest for this is that some automated measurements such as the blood pressure taken by an electronic tensionmeter and the measurements of the mobilograph can be influenced by the presence of an arrhythmia.

- Height measurement: in order to calculate BMI
- Weight measurement: weight lost over time is an important element of frailty. Obesity, on the other hand, can bear other health risks, mostly cardiovascular disease related. An electronic scale is employed.
- BMI: is calculated by the values of height and weight and will serve as a more complete assessment of body mass. Furthermore, it is necessary for the MNA questionnaire which assesses nutritional status.
- Impedance/body fat. A special electronic scale is employed. In order to do this measurement, shoes and socks have to be removed.
- Waist circumference. This measurement will serve as an index of abdominal obesity, closely related to metabolic syndrome. The measurement of waist circumference is done in the standardised way illustrated in figure 2.

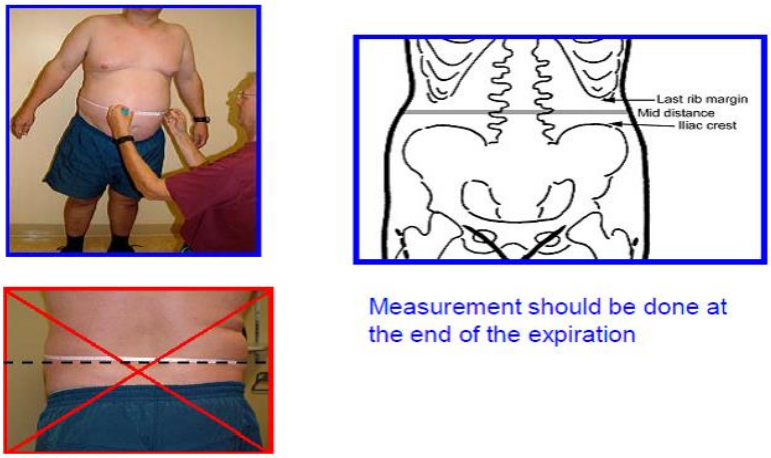


Figure 5. Waist circumference measurement methodology

- Chest circumference. This measurement serves in order to specify the right size for the WWBS device.
- Blood pressure measurements. After the subject has rested in sitting resting position during at least 10 minutes, three consecutive measurements are taken, one minute apart from one another, with an electronic tensionmeter. A mean value of the second and third measurement is automatically calculated (first measurement rejected as “trial” measurement). Simultaneously, the heart rate (HR) is measured as well.
- Orthostatic hypotension detection. After passing in standing position, two BP and HR measurements take place, one in the first and the other in the third minute after getting up. Each of these standing measurements is compared with the mean of the sitting ones. The presence of orthostatic hypotension is confirmed if the difference in systolic BP is ≥20mmHg and/or the difference in diastolic BP is ≥10mmHg. Heart rate is also evaluated in a secondary analysis to see if there is a tendency of compensation by HR augmentation. The research for orthostatic hypotension is crucial when evaluating the autonomic system function and the fall risk. The presence of the

investigator near the participant eliminates the risk of falling during the test. Measurement are done with an electronic tensionmeter.

- Arterial stiffness evaluation. These measurements are performed by the mobil-O-graph. This non interventional method bears no risks for the individual.

Table 7 summarises this sub questionnaire.

Table 7. CLINICAL EXAMINATION AND INSTRUMENTAL MEASUREMENTS

Arrhythmia detection	Pulse palpation. Is the pulse regular or not? 1. Yes=absence of arrhythmia 2. No= presence of arrhythmia
Height measurement	*In meters*
Weight measurement	*In kilograms*
BMI	Automatically calculated by the formula: BMI=weight(in kgs)/height(in meters)^2
Impedance -Body fat	*Measurement by FORA device*
Waist circumference	*In centimeters*
Chest circumference	*In centimeters*
Blood pressure measurements	3 measurements (one minute apart) in sitting position *(Mean calculation of 2nd and 3rd measurement)* *Measured by electronic tensionmeter*
Orthostatic hypotension detection	2 measures in standing position (first and then third minute)

	Comparison to the mean sitting measurement with each of the standing measurements *Measured by electronic tensionmeter* Impossibility to realize the test of orthostatic hypotension? 1. No 2. Yes Orthostatic hypotension test positive? 1. No 2. Yes 3. Test non realizable *Orthostatic hypotension present if:* *SBP differ≥20mmHg OR* *DBP differ≥10mmHg*
Arterial stiffness evaluation	Pulse wave velocity *Measured by the mobilograph* Central Systolic Blood Pressure *Measured by the mobilograph*

3.1.5 Assessment subset 5: Balance and gait evaluation

This session consists of the evaluation of mainly three functions closely related to sarcopenia (10):

- Lower limb strength.
- Balance.
- Gait speed. More than other parameters, gait speed has shown a remarkable ability to predict survival in older adults and to reflect their general health and functional status (11).

Table 8 summarises this sub questionnaire.

Table 8. BALANCE AND GAIT EVALUATION

Lower limb strength	Raise from the chair 5 times without helping from the arms *Number of seconds necessary to accomplish the task* "Test non realizable" option will be provided
Balance	Single foot station 1. <5sec 2. >5sec) 3. Test non realizable
Gait speed	Timed Get Up And Go Test *Time in seconds needed to complete the task* Speed for 4 meters' straight walk *Time in seconds needed to complete the task* *Optional open text field will be provided in order to enter qualitative evaluation of the gait, the balance, the turn and the posture*
Special conditions	Existence of a temporary condition that could affect the performance in these tests? 1. No 2. Yes *If yes, the evaluation should be repeated in another visit after the resolution of the condition.*

During this part of the clinical assessment, movement monitoring data will also be obtained by IMUs (Inertial Measurement Units) which will be attached to the subject's upper and lower limbs since the beginning of the clinical assessment appointment. The aim of this action is to record some movement, posture and activity data from these devices during the 2 hours that lasts the appointment, also in a more standardized procedure that is the gait

and balance evaluation tests. The gathering of these data will serve in the development of the WWBS (Wearable WBan System).

3.1.6 Assessment subset 6: Fried's criteria of frailty

This sub questionnaire (table 9) summarizes the criteria which are used to categorize the participants in three groups according to their level of frailty. Three out of five are based on questions done to the participants themselves, while the criterion of the gait speed is extrapolated from the previous subset "balance and gait evaluation" and the grip strength is measured with the electronic dynamometer. In the absence of any criterion the subject is characterized as non-frail, in the presence of 1-2 criteria as pre-frail and in the presence of three or more criteria as frail.

In the rare case of inadequate data to criteria identification due to lack of validity in the self-reported questions (if the person does not know or does not remember), the estimation of the physician will be employed in order to better categorize the subject, taking into account the overall findings of the whole clinical evaluation session.

Table 9. FRIED'S CRITERIA OF FRAILTY

1) Unintentional weight loss >4.5 kg in the past year	*Question to the participant:* "Have you unintentionally lost more than 4.5 kg in the past year?" 1. No 2. Yes 3. I don't know
2) <20th population centile for grip strength	Dynamometer measured grip strength (average of 3 trials, dominant hand) <u>Normal values:</u> [Men] >29kg for BMI≤24, >30kg for BMI 24.1-28 and >32kg for BMI >28 [Women] >17kg for BMI≤23 >17.3kg for BMI 23.1-26 >18kg for BMI 26.1-29 >21kg for BMI >29 Result outside the norms? Yes/No
3) Self-reported exhaustion	*Questions to the participant:* a) I felt that everything I did was an effort in the last week:

	▪ Rarely or none of the time (<1 day) ▪ Some or little of the time (1 to 2 days) ▪ Moderate amount of the time (3 to 4 days) ▪ Most of the time b) I could not get going in the last week ▪ Rarely or none of the time (<1 day) ▪ Some or little of the time (1 to 2 days) ▪ Moderate amount of the time (3 to 4 days) ▪ Most of the time Meets criteria for frailty if answer "moderate amount of the time" or "most of the time" for either question: yes/no
4) Low physical activity such that persons would only rarely undertake a short walk	Question to the participant: "Gait requiring physical activity during less than 10min per day (or 75min per week) in average"?
5) Slowed walking speed, defined as lowest population quartile on 4 minute walking test.	*Extrapolated from previous walking test.* *Abnormal values for walking 4.57 meters:* *For men; ≥7seconds for height ≤173cm and ≥6seconds for height>173cm.* *For women; ≥7seconds for height ≤159cm and ≥6seconds for height>159cm.* Is the gait speed slower? 1. No 2. Yes 3. Test not adequate (non realizable or acute debilitating condition that affects walking) *In case of acute condition affecting standard gait speed the evaluation should be repeated in another visit after the resolution of the condition.*
Categorization by Fried	1. Non frail (0 criteria) 2. Pre-frail (1-2 criteria) 3. Frail (3 or more criteria)
The case of inadequate data	Adequate data for the Fried's criteria 1. YES (if all the criteria above where answered by Yes or No) 2. NO (if we have missing data, ex gait speed non evaluable, weight loss not able to be reported etc…)

	Fried's categorization according to clinician's estimation: 1. Non frail 2. Pre-frail 3. Frail Optional free text space will be provided in order to specify special cases of inadequate data

3.1.7 Assessment subset 7: Sensory system evaluation

In this session important deficits in vision and hearing are recorded. The evaluation is based in questioning the participants themselves and the clinical impression of the examiner during the visit. The evaluation refers to any remaining deficit after correction with glasses or hearing aid. Table 10 displays this subset of the battery.

Table 10. SENSORY SYSTEM EVALUATION

Vision	*Question to the participant AND clinical evaluation/impression* *Choose the one that applies* 1. Sees well 2. Sees moderately 3. Sees poorly
Hearing	*Question to the participant AND clinical evaluation/impression* *Choose the one that applies* 1. Hears well 2. Hears moderately 3. Hears poorly

3.1.8 Assessment subset 8: Nutritional assessment

Weight loss and sarcopenia are key components to frailty. Due to various factors, older adults are at high risk for malnutrition which is related to frailty itself (12) and leads to muscle mass loss, reduced functionality, adverse health outcomes and complications and premature death (13, 14, 15).

The Mini Nutritional Assessment (MNA) is a simple tool, translated into more than 20 languages, useful in clinical practice to measure nutritional status in elderly persons. It is a well-validated tool, with high sensitivity, specificity, and reliability. An MNA score > or = 24

identifies patients with a good nutritional status. Scores between 17 and 23.5 identify patients at risk for malnutrition (16).

A short screening version (MNA-SF) has been developed (17), which, if positive, indicates the need to complete the full MNA.

In our study we are going to use the short form as a screening tool and if it gives us a score lower than 11, then the long version is applied. It takes less than 4 minutes to administer the MNA-SF and between 10 and 15 minutes for the full MNA. Table 11 summarizes this subset of the clinical evaluation and annex 5 presents the questionnaire in its original form. Translations in both French and Greek are available in the official questionnaire's web site (18).

Table 11. NUTRITIONAL ASSESSEMENT

Nutritional state	MNA short form scale for nutritional problem detection *If score ≤11 in short form, then application of the full questionnaire.* *(Annex 5)* MNA extended version *To be applied only if detection score ≤11* *(Annex 5)*

3.1.9 Assessment subset 9: Activities of daily living

The evaluation of the activities of daily living is of great importance when assessing an older adult, since it primarily reflects the level of autonomy of a person.

- Activities of daily living (ADL). The Katz Index of ADL (19) refers to performance in the six basic functions of bathing, dressing, toileting, transferring, continence, and feeding. Although no formal reliability and validity reports could be found in the literature, the tool is used extensively as a flag signalling functional capabilities of older adults in clinical and home environments (20).
- Instrumental ADL (IADL). The tool that is going to be used is the Lawton's IADL scale which is an appropriate instrument to assess independent living skills (21), more complex than basic self-care activities. The domains that are evaluated by this scale are: the ability to use telephone, to shop, to prepare food, to get along with the housekeeping, the laundry, to use the means of transportation, the responsibility for taking their own medication and to handle finances. The instrument is most useful for identifying how a person is functioning at the present time and for detecting changes over time. Administration time is 10-15 minutes. Many methods of grading

have been proposed and in the present study we will use multiple coding methods in order not to lose valuable information. Another drawback of the scale has been the "expected normal differences" in the IADL between the two genders and for that reason we intent to consider also the sex parameter when analysing the results. Despite some disadvantages, this scale is the maybe the most widely used in research and clinical setting.

Table 12 summarizes the components of this subset of the clinical assessment, whereas annexes 6 and 7 present the exact questionnaires. Translations of the two questionnaires exist in both Greek and French (22).

Table 12. ACTIVITIES OF DAILY LIVING

Activities of daily living	Katz Index of Independence of ADL *(Annex 6)*
Instrumental activities of daily living	Lawton IADL scale *(Annex 7)*

3.1.10 Assessment subset 10: Cognitive, mood and sleep evaluation

This session includes the following parts:

- Global cognitive function evaluation. The Mini Mental State Examination (MMSE) test is employed (23), (annex 8), available in translated and validated versions in both French and Greek (24, 25). This scale is the most widely used instrument of global assessment of cognitive function both in clinical, epidemiological and research settings. It is useful as a screening tool in order to detect a cognitive dysfunction and to follow up its evolution, but it lacks specificity to distinguish between certain forms of dementia and sensitivity to discriminate a mild dysfunction in an early stage (26). Moreover it is highly influenced by the age and educational level (27, 28). A cut off score of below 24 during the first evaluation is used as an exclusion criterion for the present study, in order to avoid recruiting participants with important cognitive problems who are less likely to be able to use in an optimal way the FrailSafe system's devices and applications and to be apt for the follow up period.

  To overcome the inherent inability of MMSE to detect more discreet cognitive dysfunctions and to augment the sensitivity of cognitive testing in highly educated older adults, the Montreal Cognitive Assessment (MoCA, annex 9) is also employed. The latter is a brief cognitive screening tool for the detection of MCI (29, 30, 31), available in multiple languages, among which the French and Greek. Since MCI is an important morbidity for our study, this scale will contribute to its detection.

- Memory complaint's detection. The expression of a memory complain from an older subject could be an indication of early sings of cognitive dysfunction (32), although there is not global consistency in this finding in the literature (33). Still, the general tendency is that subjective memory complains merit further evaluation (34, 35).
- Depression screening. The 15-items' Geriatric Depression Scale (GDS) (36) (annex10) is used in order to detect subjects with possible depression. This scale cannot pose the definitive diagnosis of depression, even though there is some evidence that it can detect a major depressive episode (37). Still it can be used to screen for depressive symptoms (38). It is available in both Greek in a validated version (39) and in French (40).
- Sleep problem. This pathology is investigated through questioning to the individual and also assessment of any special hypnotic treatment.

The sub questionnaire of this session is summarized in table 13 and annexes 8-10 contain the complete tests.

Table 13. CONGITIVE, MOOD AND SLEEP EVALUATION

Cognitive function	Scale MMSE (Mini Mental State Examination) *(Annex 8)* Scale MoCA (Montreal Cognitive Assessment) *(Annex 9)*
Memory complain	*Question to the participant:* "Do you have the impression that your memory works less well in comparison to the people of your age?" 1. No 2. Yes
Depression	Geriatric Depression Scale- 15 items (Annex 10)
Sleep	*Choose the one that applies* *The need of medication to sleep correspond also in a sleep problem* 1. No sleep problem 2. Occasional sleep problem 3. Permanent sleep problem

3.1.11 Assessment subset 11: Self-evaluation scales

The last session of the clinical evaluation battery aims at quantifying some subjective aspects of health perception and quality of life in general. It includes evaluation of:

- Health state: the person is asked to self-rate his/her health condition in respect to his/her age, giving a grade from 1 to 5, which corresponds to qualitative characterization of their health self-perception from very bad to excellent. Afterwards, a comparison to the past year is also requested. These two items are taken from the SF-36 questionnaire (41).
- Quality of life (QoL) self-rating: the question emphasizes the general aspect of QoL and not merely the "health related QoL". A visual analogue scale (VAS) in vertical orientation is employed and the person is asked to put a mark in the level that corresponds to his/her estimation.
- Pain self-evaluation: the assessment of pain is a central element of the evaluation of the older subject. Pain, which sometimes rests under-expressed, underdiagnosed and undertreated, can have devastating consequences in the physical and mental well-being of a person. A visual analogue scale (VAS) in vertical orientation is employed and the person is asked to put a mark in the level that corresponds to his/her estimation.
- Anxiety self-evaluation: A visual analogue scale (VAS) in vertical orientation is employed and the person is asked to put a mark in the level that corresponds to his/her estimation.

Both VAS (42, 43) and one-item self-rating evaluation systems (44, 45) have shown satisfying validity in personal perception measurements, even in older adults, comparable to those of more extended scales. Table 14 summarizes this subset of the battery and annexes 11-13 illustrate the actual VAS that are used.

Table 14. SELF-EVALUATION SCALES

Quality of life self-rating	*Visual analogue scale (Annex 11)* "In generally, and not only referring to your health, how would you grade the quality of your life?"
Health self-rating	"In generally and according to your age, how would you rate your health from 1 to 5, where 1 means very bad and 5 means excellent?" *Check the one that applies* 1. Very bad 2. Bad 3. Medium 4. Good 5. Excellent "Comparing to a year ago, how would you rate your health

	now?" *Check the one that applies* 1. A lot worse 2. A little worse 3. About the same 4. A little better 5. A lot better
Pain self-evaluation	*Visual analogue scale (Annex 12)* "Please mark on the line the point that you feel better represents your perception of your current state about pain."
Anxiety self-evaluation	*Visual analogue scale (Annex 13)* "Please mark on the line the point that you feel better represents your perception of your current state about anxiety."

3.2 Data regarding social interaction and natural language analysis

An interesting aspect of the FrailSafe approach proposed is the text mining component that is based on the written scripts and the social interaction of the older adult using social media which will try to capture their personality and their current emotional state and possibly correlate (via machine learning approaches) the word usage and the social media behaviour of older adults to frailty symptoms. In order to proceed in this analysis natural language sentences need to be collected, personality traits need to be recognized and the social media interaction need to be explored.

3.2.1 Collection of written text for natural language analysis

The Natural Language Analysis (NLA) component of FrailSafe aims to detect signs of cognitive deficiencies in written text. Especially for determining a person's mental state, a textual input is more significant than a speech utterance, since the latter can be distorted by many unrelated factors that can produce false positives when searching for mental peculiarities. Given a textual input, then spelling errors, syntactic discrepancies, and semantic misinterpretation are just a few indicators that when combined with a personalized user model that stores information about the educational level of an individual or its previous linguistic state, can allow the tool to trigger alerts. These alerts could be distributed

appropriately (e.g., to the writer, to his/her relatives, to his/her doctor, etc). Over time the person's use of the language evolves, but since this process is very slow, sudden out-of-the-norm inputs will also be able to trigger alerts.

In the beginning of each participant's recruitment, samples of text written by her/him will be collected, preferably in electronic typed (UTF-8) format. If this is not possible, other modes of written text (e.g. handwritten text, dictated text to one of the personnel's member, etc) will be collected and converted to typed UTF-8 format, each with a tag mentioning the mode of original input. All collected texts will be registered to the database for analysis after the permission of the individual. The security and confidentiality of personal data will be reassured by the structure of the database (see section 5: Ethics and safety).

In practice, we ask the participant to show us a sample of their old writings (preferably e-mails, Word documents, etc). The second step is collecting text from the present moment. In order to stimulate the participant's inspiration, possible subjects for writing are provided in the questionnaire, but this is by no means restrictive to the person's choice of what to write. Finally, a picture (annex 14) is provided in order for the participant to describe what is illustrated there. The written text collection task is given to the participant to prepare at their home, except in case where they are unable to write themselves, so it will be dictated during either the clinical evaluation or the home visit. If the person is capable of preparing the texts him/herself, an instructions' sheet is delivered to them (annex 15) and it is collected filled in during the nurse's home visit. Table 15 describes the instructions to the clinician for written text collection.

Table 15. Data collection of written text (first time)

Step 1	Ask for previous text (e-mails, letters, etc.). *Preferably typed (else handwritten)* *Either we have already asked the participant to bring with him some old text when (s)he comes to the clinical evaluation appointment, OR we ask him/her to prepare something to show to the person that is going to realize the home visit, OR we ask him/her to send them via e-mail if they have the ability to do that.* *If electronic typed text is not available, then photos of available texts should be taken, after the consent of the person, paying also attention in the "sensitive" character of some types of documents.*
Step 2	Ask to think of a major life event and to write it down. *If possible typed (by preference), otherwise handwritten. If not possible dictated.*

	Ask to think of a recent, everyday life routine, e.g. write what he/she did in the previous day (this is a question that will be repeated in future sessions as well, since it produces valuable differential data for each individual). Ask to think a major enjoyable life event, although unpleasant events should not be dismissed. For instance: • Wedding • Child's birth. • Children's achievements • Enjoyable travel experience. • Professional achievements. • Last time you felt excitement about a forthcoming event.
Step 3	Show attached picture and ask to describe it in written text *(Annex 14)* *If possible typed (by preference), otherwise handwritten. If not possible dictated.*

After the first written text collection, new samples of written text arecollected in each clinical visit, according to the second step's model:

Table 16. Data collection of written text (in every clinical assessment after the first)

Ask to think of a major life event and ask to write it down. *If possible typed (by preference), otherwise handwritten. If not possible dictated.* Ask to think of a recent, everyday life routine, e.g. write what he/she did in the previous day. Ask to think a major enjoyable life event, although unpleasant events should not be dismissed. For instance: • Wedding • Child's birth. • Children's achievements • Enjoyable travel experience. • Professional achievements. • Last time you felt excitement about a forthcoming event.

Annex 14 presents the picture that the participants is asked to describe, while annex 15 contains the sheet that is given to those who are capable to fill in the written text themselves at their homes.

For the collection and the management of the data related to written text, the physician or nurse will use one of the mobile devices given to their use by the study and a special application for scanning, storing and sending documents centrally to the database system.

Natural language analysis will employ both statistical and informational based methods of text mining / machine learning in order to reveal information concerning the individual's mental state from their writings. Specifically, the process of text writing will be treated as a Hidden-Markov Process, where the person's mental state evolves over time but we do not have direct data on this evolution, but only indirect evidence (the written text) that can reveal the (hidden) mental state. Therefore, each piece of text will undergo a series of tests/transformations, i.e:

- tf-idf statistical filtering
- bag-of-words transformation
- cosine-distance cross-comparison with other samples
- headword/keyword sentiment analysis
- entropy estimation
- redundancy estimation compared to other samples
- syntactic parse quality test

The methods that will be employed will be specifically trimmed in order to cope with small size texts as are the samples that we are expecting to collect. The evolution over time of the above characteristics, as well as the cross-comparison with the metrics of other individuals in the general population will enable us to automatically detect any irregularities in the written text samples.

3.2.2 Self-administered questionnaires

Since the majority of the now-aging European population is technologically literate, many people may use social media like Facebook, Twitter and other publicly-available fora and chat-rooms to communicate with friends and relatives. Even short messages posted there can provide valuable information concerning the writer’s mental and emotional state, not to mention the new means of communication aspects that they provide. In order to collect information regarding social media use the Social Media Questionnaire are employed (annex 16).

Moreover, to identify personality traits we employ the most widely known model of personality trait qualification, the Big Five questionnaire (annex 17). According to Big Five, the human personality is described as a vector of five values of traits. The combination of Big Five personality dimensions explains the dynamics of a personality. For example, a person

may be very talkative (high Extraversion), not very tolerant and sensitive (low Agreeableness), systematic and punctual (high Conscientiousness), easily anxious (high Neuroticism) and extremely curious (high Openness). This personality characterization will be automatically extracted and taken into account in the frailty metric. In addition it will help in improving the services proposed by our approach to the individual according to his/her personality and current emotional state.

Similarly as the written text collection, these two questionnaires are delivered to the participants in order to fill them up themselves in the beginning of their recruitment, typically, during the first clinical evaluation visit. After completion of the questionnaires, the sheets are handed back by the participant to a study's member during their next programmed appointment, typically to the nurse during the FrailSafe system home visit. In opposition to the written text collection, which will be taking place during each clinical evaluation session all over the duration of the study, the social media and big five questionnaires are answered only once, at the phase of the subject's recruitment.

3.3 The (phone) follow up questionnaire

After the first evaluation triplet takes place (clinical assessment appointment, FrailSafe system home visit and blood sampling), the follow up by a short battery of questions (table 17) monitors the occurrence of adverse events like falls, fractures, hospitalisations and/or death. This follow up, which is programmed for every 3 months' time, will be done either by telephone or incorporated in a coinciding FrailSafe system home visit or clinical assessment appointment.

These outcomes, which represent main complications of frailty, triggering factors for shifting from one frailty level to another and potential prevention goals, are also defined as the study's hard outcomes (section 5.1).

Table 17. Follow up questionnaire

Falls	Did any fall occur?	Yes/no
	Number of falls	
	Date of the event	
Fractures	Did any fracture occur?	Yes/no

	Date of the event	dd/mm/yyyy
	Anatomic location	*Click all that apply:* ○ upper limps ○ hip-pelvis ○ vertebral ○ other ○ multiple factures *"I don't know" option also provided*
Hospitalizations	Did any hospitalization occur?	Yes/ No
	Date	dd/mm/yyyy
	Length of hospital stay (in days)	+option of "still hospitalized" provided
	Outcome	○ totally cured ○ amelioration ○ stability ○ worsening of general health state ○ death ○ institutionalization ○ still hospitalised
Conditions of hospital recours	○ programmed hospitalization ○ visit to the emergency care room by release without hospitalisation ○ urgent hospitalization	
Death	Did death occur?	Yes/no
	Cause	Open field for the cause of death +option of "I don't know also provided"
	Date	dd/mm/yyyy

In a six months' basis, this questionnaire will be completed with the ADL/IADL questionnaires (Annexes 6 and 7) in order to evaluate the functionality in the activities of daily living, therefore the participant's autonomy level.

3.4 Evaluation of the subject's housing conditions

Housing conditions, both indoors and outdoors, may represent an important factor of autonomy maintenance or restriction. Moreover, unsuitable environmental conditions can contribute to a person's frailty and raise the risk of falls and mobility restriction.

The assessment of environment and amenities is done on the spot, meaning the participant's house during the FrailSafe system home visit. Both the individual's and the visitor's opinion will be recorded (table 18). The evaluation of housing conditions is done during the first and the last FrailSafe system home visit for groups A and B and only during the first FrailSafe home visit for group C. Group D has no home visits programmed, so no housing evaluation will take place.

Table 18. Housing conditions' evaluation

Habitation zone	1. Rural 2. Semi-urban 3. Urban
Housing/ surroundings	Does the person think that their housing environment is suitable and adapted to their needs/particularities? 1. Yes, 2.No *If NO, please note all that applies :* 1. unsuitable/ inconvenient in-house facilities/ surrounding , 2. unsuitable/ inconvenient/ too distant environing facilities Does the visiting health care professional estimate that the housing environment is suitable and adapted to the

	participant's needs/particularities? 1. Yes, 2. No *If NO, please note all that applies :* 1. unsuitable/ inconvenient in-house facilities/ surrounding , 2. unsuitable/ inconvenient/ too distant environing and outdoor facilities 3. hygiene conditions How many stairs has someone to climb in order to access the house? *(floor levels accessed by elevator not included).* *Enter the number*

3.5 Blood tests

In the beginning of the study, along with the first clinical assessment appointment and the first FrailSafe system home visit, a blood sampling will take place for telomeres measurement. After following a standard sampling procedure, all samples will be sent and processed in INSERM's laboratory in Nancy, France, along with their traceability accompanying form (Annex 18). Telomere length will be measured in DNA extracted from white blood cells, with the southern blot method (46) which is the most reproducible method for measuring telomeres length (47).

Presence of short telomeres is associated with various age-related degenerative diseases (48, 49). Recent studies indicate that short telomere length is not only a biomarker but a significant bio-determinant of such diseases (46, 49). The present study will assess the hypothesis that measurements of telomere length may provide further information in the characterization of frailty in older subjects.

A second blood taking will be realized only in the center of the University of Patras in M27 for group A, in M25 for group B and in M35 for group C. The immune system alterations observed in frailty are multifaceted and associated with increased morbidity and mortality in older adults (50, 51). The identified alterations include heightened inflammation and alterations in the innate and adaptive immune systems. The heightened inflammatory state includes increased levels of inflammatory molecules (IL-6 and CRP) and increased counts of

white blood cells and their subpopulations. These changes may play an important role in the pathogenesis of frailty, directly or through its influence to other physiologic systems (52-54). A subgroup of participants, men and women in UoP, will be tested for their immune system and inflammatory profile, vitamin D levels, and endocrine system function (54)(IGF-1, sex hormones). Complementary biological tests can be proposed according to newest data of the international literature in the field of frailty and the availability of biological material. The aim of the study is the analysis of immunological changes during senility and age-related markers of inflammation which may provide useful prognostic markers of morbidity and mortality. The characterization of elderly people with higher risk factors might allow for preventive and/or therapeutic measures to assure successful ageing and survival and to stem the rapid progression of the ageing process.

3.6 Other investigations

These investigations, as mentioned in the DoA, will be conducted only in the clinical centre of Patras.

3.6.1 Autonomic nervous system tests

The autonomic nervous system (ANS) controls the smooth muscles of the internal organs, the cardiovascular system and the functioning of the secretory glands and plays a major role in the regulation of the physiological processes of the human organism during normal and pathological conditions. Among the techniques used in its evaluation, the heart rate variability (HRV) has arising as a simple and non-invasive measure of the autonomic impulses, representing one of the most promising quantitative markers of the autonomic balance. Heart rate variability reflects the changes in the interval between heart beat (R waves) over time. Time between one R wave and the next, in milliseconds, is termed the R–R interval. The ANS governs the R–R interval via the sympathetic and parasympathetic pathways (55). The relative dominance of either pathway over the other represents an alteration in the sympathovagal balance which is reflected in R–R changes (56). Under normal resting conditions in healthy individuals, it has been suggested that the parasympathetic pathway is dominant, resulting in a high HRV (57), while lower HRV and poor health has been linked to increased sympathetic activity at rest (58,59). There are many factors that can influence HRV such as mood, alertness, mental activity, gender and age (60-62). Although the research relating to gender differences is controversial (59, 62, 63), the relationship between age and HRV has been well documented (59, 61, 64, 65). Low HRV is associated with progressing age and with an increased risk of cardiovascular mortality including sudden cardiac death, in clinically disease-free patients (65).

The aim of the ANS testing is to investigate the impact of frailty in the cardiovagal control of elderly people over 70 years old. Therefore 20 participants from each group classified according to Freid's criteria, as non-frail, pre-frail or frail, equal number of men and women, will be examined in a battery of neurophysiological tests: time domain analysis of RR interval variation during normal and deep breathing (DB), Valsalva manoeuvre, and tilt test. At the same time, the ICT FrailSafe partners have being working to adapt a technique, which measures HRV by using colour channels in video recording to extract the blood volume pulse from the facial region. The participants' tablets will be used for this purpose recording signals whilst playing with game applications.

The neurophysiological study will be carried out in a quiet, air-conditioned room. A two-channel Counterpoint, MedtronicDandec apparatus (Medtronic-Dandec Electronics, Sakovlunde, Denmark) will be used. The electrodes on the transmitter will wet with water and placed on the chest against bare skin to ensure good skin contact. Each participant will be instructed to remain relaxed in the recumbent position throughout the recordings except during the tilt test. Intervals of 5 min between tests are allowed in order that Heart Rate (HR) could return to baseline levels.

The neurophysiological profile will be determined by the following measurements:

1. RR interval variation with respiration (sinus arrhythmia) under two conditions: RR intervals during 1 min of normal breathing (Rest RR) and 1 min of controlled deep breathing (approximately 6–7 respiratory cycles per min) (DB RR); the results are expressed as a percentage of difference maximum–minimum RR interval divided by mean RR interval. HR (beats／min) during both testing conditions will be also recorded.

2. Valsalva maneuver: ratio of the longest RR interval during phase IV to the shortest RR interval during or immediately after blowing to maintain a column of mercury at 40 mmHg for 15 s (phase II or III).

3. Tilt test: ratio of the RR interval at 30 s to RR interval at 15 s after sudden change from supine to standing position.

To ensure the reliability of the test, each autonomic test will be repeated two to five times with 5-min rest period between trials.

3.6.2 Sarcopenia profile

In a study of frailty, sarcopenia should be accounted for. Although frailty and sarcopenia, are distinct conditions they interact and share similar risk factors and possibly similar pathophysiological mechanisms which lead to similar adverse outcomes (66). At the 18th month of evaluation a subgroup of participants, 40 men and women in UoP, will undergo a MRI (Magnetic Resonance Imaging) scan or DEXA (Dual energy X-ray absorptiometry). The aim is to provide a profile for sarcopenia to correlate with FrailSafe data.

DEXA is a measurement indicated for instrumental confirmation of low muscle mass (67). It is based on the notion that when a beam of X-rays is passed through a complex material, the beam is attenuated in proportion to the composition and thickness of the material. The DEXA scanner emits two X-ray beams comprised of photons at two differing energy levels and as a result of the interaction within the human body, the incident X-ray photon energy is exponentially attenuated. By knowing how many photons are transmitted with respect to the number detected, the amount of bone mineral and soft tissue (fat and fat-free mass) can be determined. Notable advantages of DEXA include low cost, speed of measurement (whole-body scans require less than 20 min) and exposure to low levels of radiation.

Accurate measure of both anatomic and fat-free skeletal muscle can be obtained with magnetic resonance imaging (MRI) (68). Typically, this method provide regional estimation of skeletal muscle by means of cross-sectional images, which allow also to detect muscle infiltration from adipose tissue and to quantify fat-free skeletal muscle. Total muscle area and fat-free skeletal muscle area, calculated from cross-sectional images, can be integrated from head to toe.

3.7 Overview of sensor devices: the FrailSafe system

The FrailSafe study aims at investigating and specifying appropriate physiological and behavioural characteristics that can be used for defining biomarkers of frailty that can be of a significant predictive value. The FrailSafe system consists of an aggregation of sensors of biological parameters that are known or may prove to be relevant to the frailty's phenotype.

All throughout the duration of the study, mostly in its first part, these sensors will be tested for their efficacy in predicting frailty related outcomes and for their comfort and feasibility for wide base use.

It is important to point out that the devices constituting the FrailSafe system are used during each phase of the study according to their availability. Thus in first months only a part of them are ready for use, while afterwards new versions and more material will be added.

During the FrailSafe system application periods of groups A and B, participants will receive a telephone call each day by a member of the investigation team. The purpose of this phone call is double:

Il the first stage, when groups A and B are tested, the daily phone-call aims at identifying possible recurrent events that happened during the FrailSafe session period. By this way, any "event" or symptom reported in such a short notice, could be mapped and assigned to a specific signal obtained by the FrailSafe devices, in order to test their sensitivity and validity. Additionally, since the study is still in the initial experimental phase and the material not yet

developed in perfection, this daily phone call during the FrailSafe session also verifies the correct usage of the material, identifies potential problems, adressed possible questions and resolves potential issues. Moreover, it will serve as a measure to reassure the older people about the probable difficulties that they will encounter facing for the first time unknown material and dexterity learning challenges.

Although we are aware that by the mere fact that we are observing a phenomenon, we can partially influence it, we judge that, at least in the initial phase of the program, the benefits from our phone intervention outweigh the risk of biases' insertion. Similarly we deal with the potential "hidden" stress factor that the application of the FrailSafe system may pose to the participant: we believe that the possible benefits overcome the inconveniences, especially when we are generally referring to "healthy" people (since frailty is not a disease) who have chosen to participate in the study.

In the second phase of the study and during the group C's testing, it is not expected to have the need of a daily phone call, since the majority of technical issues are expected to have been addressed. However, being always in the context of a clinical study, the possibility will be given to the participants to call us themselves if there is need.

Even though the description of the final commercialized project overcomes the scope of the present deliverable dedicated to clinical study's methodology, the consortium intents to make use of the questions and problems raised by the daily phone calls during the FrailSafe session, by collecting the most prevalent ones and constructing a Q&A leaflet or even proposing a help line for the phase of the final product's exploitation.

[This daily phone call during the FrailSafe system's application should not be confused with the phone follow up, which will take place every 3 months (figure 1). The purpose of the latter is to follow the subjects up for hard outcome events that interest us for the study's objectives and is addressed by either a phone or an in person administered questionnaire.]

In case of serious equipment malfunction or other issues that prevent the collection or transmission of data during the initial phase of the field studies, there will be visits to participant's home to correct the problem. The status of data will be monitored automatically.

3.7.1 WWBS (Wearable WBan System)

WWBS is a new wearable solution, similar to a vest in appearance, which takes its origin from an already developed product of Smartex, WWS (Wearable Wellness System), with a further integration of some Inertial Measurement Units (IMUs) in order to have information of higher quality with regards to movement analysis. Biological parameters that are going to be monitored by the WWBS system are:

- heart rate
- heart rate variability (probably in post processing)

- respiratory wave
- respiratory rate
- posture
- physical activity classification and
- steps per minute

WWBS will be used for long term monitoring of the aforementioned parameters in a continuous basis during the FrailSafe system home visit sessions for as long as the participant carries the vest. This duration depends on each individual's convenience and tolerance of the system and the WWBS's energy autonomy features, but participants are encouraged to use it as long as possible. It is initially presented to the participant by the nurse that visits his/her home during the programmed FrailSafe system home visits according to the programmed time schedule for each group. She explains to the subject its use and rational, demonstrate the practicalities of its putting on and off and give instructions of how to resolve any practical issues that may come up. During the initial phase of the study, the participant is encouraged to contact each centre's reference person in case (s)he has questions to ask and to take off the WWBS if for any reason (s)he feels uncomfortably. Telephone follow up by the study's nurse is repeated on a daily basis to catch up will the WWBS experience. Even if there is no clear interaction with pacemakers, the use of the WWBS will be avoided in people carrying pacemakers or external electrical heart stimulation devices.

Since the WWBS will not be fully developed before M15, for the first months of the study other solutions (such as straps around the chest to monitor heart and respiratory rate) are used.

The postural, movement and activity analysis will be performed by commercial product(s) integrating some IMUs attached to the participant's upper and lower limbs and maybe chest and back. The installation of IMUs for the initial part of the study will be done during the clinical evaluation appointment. By this means, data will be obtained during the approximate 2 hours of the appointment, including also movement data from the gait and balance tests. The WWBS version will provide IMUs incorporated in the vest's body for the monitoring of the trunk movement. Whether or not limbs' IMU solutions should also be provided will be decided according to the first results derived from the upper and lower limbs IMUs' recordings from the study's initial phase.

3.7.2 Blood pressure monitoring

Apart from the measurements of blood pressure incorporated in the clinical assessment session, arterial pressure monitoring will take place in participants' house as well. An electronic tensionmeter (FORA device) will be lent to every participant during the FrailSafe system home installation, with the instructions to measure his/her blood pressure twice a

day. After at least 5 minutes of rest, with an empty bladder and before breakfast or dinner or any drug intake, a set of 3 successive measurements will be taken, beginning in seated position and afterwards after one minute of standing, morning and evening. Using FORA's device both patients and doctors can obtain triplicate readings with the ease of pressing one button. The FORA application also allows the Bluetooth-enabled FORA devices to transmit the results instantly to iOS and Android devices.

3.7.3 Dynamometers

The dynamometers will be used in 2 ways. First, during the clinical assessment appointment, measurement of grip strength will be obtained for classification to frailty categories according to Fried's criteria.

Secondly, the dynamometers connected to a special tablet games will serve as a means to get participants test their muscle strength regularly (as well as exercise), in a more pleasant way. We suppose that they are going to be more motivated in their regular muscle strength exercise if the method of gamification will be employed. So we will devise an intervention system that hooks up the dynamometer to a video game that responds to the patient's use of it: if patient is doing his/her exercises correctly, then (s)he does well in the game. For example, in one game patient's dynamometer may control a hot air balloon or a bird going up and down, avoiding obstacles on the map. Evaluation of mean and max strength values over time will serve as monitoring for the participant's progress and evolution. Participants will be encouraged to play their dynamometer/tablet games as often as they wish, ideally at least once a day.

The rationale behind this measurement is that muscle strength is closely related to sarcopenia and therefore to frailty (69). Muscle strength measures of different body compartments are correlated, so when feasible, grip strength measured in standard conditions with a well-studied model of a handheld dynamometer with reference populations can be a reliable surrogate for more complicated measures of muscle strength in the lower arms or legs (70, 71).

3.7.4 Indoor monitoring sensors

A part of the lifestyle information of older people will be acquired through physical activity monitoring with tracking systems. In this respect, an indoor localization system using beacons will be developed, in order to monitor the people's movements and habits within their homes.

In particular, beacons will be placed in places within their home which are important to be monitored, such as the bedroom, the kitchen and the toilette. We initially tend to investigate activity in these areas because of the relatively greater importance of these rooms' related activities. Monitoring movements in the bedroom will give us an idea of sleep

behaviour, in the kitchen of alimentation occupation and in the toilette of bladder and bowel habits. Further processing of these kinds of data can reveal activity-related information, such as which rooms the person spends most time in, how much time he/she spends in each room, frequent patterns of movements, etc.

As the person moves in the room, carrying around their smartphone, the application will regularly “communicate” with the nearest beacon, as well as recognize the distances from all beacons. The data collected can be used to extract both the room-level position and the exact coordinates of the person in the whole space. To facilitate the constant attachment of the smartphone, which will get in contact with the beacon, with the individual, various types of smartphone cases will be purchased by each centre and proposed as alternatives to the participants. By this means the participant will be able to carry his/her smartphone attached around his/her neck, arm or waist, according to preferences and convenience.

The placement of the beacons in target areas requires no technical expertise and will be done by the nurse during the FrailSafe system home visit. She will just have to stick or place them in the proper places and note the coordinates of each one of them.

Some guidelines for the proper positioning of the beacons in the rooms are the following:
a. One beacon should be placed per room. A "room" does not necessarily correspond to the architectural definition but rather to the logical one that correspond to its use.

b. Within each room, the beacon should be placed, if possible, in a central position, in order to cover as much of the room's space as possible, while at the same time being as much separated from the other rooms as possible. The placement should be such that when the person is in a room, there is no ambiguity about this room's beacon being the closest one to the person, compared to the beacons in other rooms. If the beacon cannot be placed in a central position, it should be placed in a position that is far from other rooms of interest, in order to avoid any false measurements.

c. Concerning installation, the beacons can just be put on the floor, e.g. under a table or under a couch, or stuck to a wall, or even to the ceiling, if possible. It would be best if they are stuck even when they are put on the floor, in order to avoid them being accidentally displaced. Stickers will be provided with the beacons in order to easily install and uninstall them.

d. Proximity to metallic objects (like metallic bed frames), water and microwave oven should be avoided when possible in order to avoid signal interference.

Beacons also monitor ambient temperature.

3.7.5 Mobile devices

Tables and mobile phone play a crucial role in the FrailSafe system installation and function. They act as the central node of data acquisition and management.

By their incorporated sensors (accelerometers, gyroscopes, pedometer, GPS etc.) they gather data regarding the user's location, mobility and activity profile.

Moreover they will serve as the means to play virtual reality (VR) / augmented reality (AR) games which will provide us with meaningful quantitative metrics (table 20), in order to evaluate, quantify and follow up over time cognitive functions and behavioural patterns. AR games are presented in more detail in the next section. In VR/AR games/rehabilitation programs the user is connected to the VR system as part of the input/output loop, allowing individuals to provide input to the virtual environment (VE) and experience the result of that input, meaning that the individual can either see a feedback.

Also the dynamometer exercises will be connected to the tablet.

Table 19. VR games quantitative metrics

- *Played the game?*
- *How often (Number of times/block)*
- *Success rate (Attempts to start playing but not played)*
- *Mean reaction time*
- *Mean Duration*
- *Mean Time of pauses*
- *Number of pauses/block*
- *Events triggered*
- *Concentration index*

During the FrailSafe system home visit the nurse trains the individual in the use of tablets and smartphones, demonstrates and verifies the comprehension of game playing and emphasizes the importance of carrying the smartphone on them constantly with the help of special cases provided to them for this purpose. The participants are encouraged to carry the smartphone on them continuously and to use the tablet for game playing and dynamometer exercising as frequently as possible. Finally, participants are trained in the devices' battery charging and the nurse verifies the full charging of all devices in every home visit.

3.7.6 Augmented reality serious games (ARSG)

FrailSafe will rely on the augmented reality (AR) gaming concept offering both clinical assessment and rehabilitation options, usually not available with traditional rehabilitation methods. It aims exploiting vision technologies to provide older people with assistive visual

feedback while performing games/rehabilitation as well as medical staff with biomechanic indicators for assessment and diagnosis support. Moreover, the AR gamer environment motivates the individual and makes him/her train more often and for a longer period of time without getting tired. The continuous feedback provided by the AR therapeutic programs builds and strengthens his/her motivation.

The AR glasses will provide to the study participants the opportunity to test the augmented reality serious games (ARSG) for both diagnostic and maybe therapeutic reasons. In contrast to VR, AR superimposes a computer-generated image on a user's view of the real world. The interest lies in the fact that we can close the loop between interventions and behavioral measurements. So by using a game where walking on a synthetic red line on the carpet will be demanded, measurements of instabilities and gait properties will be performed. At the same time, the idea is to create a navigation AR game that will motivate the older adults to increase their mobility by setting goal-driven scenarios such as short-distance (walk to the wall) and long-distance ones (follow the 'virtual' line for 100 meters).

The AR glasses will be delivered by the nurses during the FrailSafe system home visit and explication of their use and objective will be given. Training for ARSG playing will also be handled by the nurses, as well as assistance during the standing mobility challenges. Additionally, a training application will be provided where the user will look around and investigate virtual objects. In the case of seated alternatives of these games, individual training as often as possible will be encouraged.

Although the use of the AR glasses was described since the begging of the study, their actual feasibility of use by this study's participants and under given conditions, is still an issue of discussion and reflexion among the Consortium.

3.7.7 FrailSafe system experience satisfaction interview

At the end of each FrailSafe system home visit a short interview of satisfaction is administered to each participant. The aim is to test the FrailSafe system's ease of use, identify any practical difficulties the participant experienced in its handling in the home settings and evaluate the individual's acceptance. The participants' remarks will be taken into account for the developing and amelioration of the FrailSafe system.

3.7.8 FrailSafe system's application standardization

As predicted by the initial proposal and its amendments, not the totality of the FrailSafe system devices was available since the beginning of the clinical study.

Therefore, we noted a quite important heterogeneity among the first FrailSafe sessions conducted in the centres of Patras and Cyprus. In order to address this source of bias, the

very first participants for whom the FrailSafe session was incomplete according to some minimum requirements (enlisted bellow), will be called back in order to repeat the session.

The FraiSafe system devices which are currently available and are going to be used in all FrailSafe sessions (=home visits), from now until new versions of devices arrive, are:

- The tablets with virtual reality games (for all participants)
- The smartphones with the GPS application (for all participants)
- The blood pressure monitoring devices (for all participants)
- The WWS devices (strap version) (for 1 participant at a time)
- The dynamometers for grip strength games' playing (for all participants)
- The beacons (for all participants).

Towards the direction of standardizing the procedures and adapting the material to the actual needs of the participants, working documents treating practical issues such as study's material, anticipated and actually occurring problems and procedures have been generated and are being constantly updated. Similarly, detailed check lists about the material, requirements and conditions to be verified before, during and after the clinical evaluation and the FrailSafe home visits have been distributed in the 3 clinical centres (Annex 19).

4. Operational procedures per group

In a more concentrated and systematic way the operational procedures per group are as following:

4.1 All groups

1. Quick first verification of inclusion and exclusion criteria
2. Randomization to groups (only applicable for group C and D)
3. Informed consent and attribution of a unique ID number
4. First part of clinical evaluation session: questionnaires to verify inclusion and not inclusion criteria, Fried's criteria of frailty, medical history and cognitive assessment will be administered (tables 4, 5, 6, 9, 13).
5. Second verification of the inclusion/exclusion criteria according to the first part of the clinical evaluation's results. If exclusion, replacement of the participant and repetition of steps 1-5 for the next candidate

The steps from this point down and their time programming will differ according to group allocation.

4.2 Group A- Start Up group:

1-5. As described above for all groups

6. Complete clinical evaluation session (tables 7, 8, 10, 11, 12, 14) (M≥6)
7. Data collection regarding social interaction and natural language analysis:
    - Data collection of written text for the first time (table 15), where the participant will either be helped to provide text by dictation or be asked to prepare it him/herself in his/her home and deliver it to us in the next appointment and
    - self-administered questionnaires The Social Media (annex 16) and the Big five (annex 17) questionnaire will be given to participants in order to fill them in themselves and deliver them to us in the next appointment
8. First FrailSafe system home visit (M≥6):
    - Blood sampling for telomeres
    - Fill in the evaluation form regarding the participant's housing (table 18)
    - Collect any questionnaires filled in by the participant since the last visit: written texts, social media and big five questionnaires
    - Complete any missing information of the clinical evaluation (i.e. scanning of a forgotten prescription, scanning of an older written text provided by the participant, write down dictated text)
    - Installation of the currently available FrailSafe system and explication of the use, the purposes and the technical issues of the FrailSafe material. Verification of its correct function
    - Provide contact details and instructions in case of any help needed
    - Set the next appointment to retrieve the FrailSafe material (5^{th} day)
9. Maintenance of the FrailSafe system at home during 3-5 days
10. Daily phone calls during the instauration of the FrailSafe system to catch up with the experience of the use of the material and any problems that may have arisen
11. Short satisfaction interview in the day of FrailSafe system retrieval
12. Telephone Follow-up after the retrieval of the FrailSafe in a 3 months' basis (table 17). (M9-M24)
13. Second clinical evaluation (M27) (tables 5-14)
14. Data collection of written text after the first time (table 16) (M27). The participant will either be helped to provide text by dictation or be asked to prepare it him/herself in his/her home and deliver it to us in the next appointment
15. Second FrailSafe system instauration (M27)
    - [Only for Patras]: blood sampling
    - Fill in the evaluation form regarding the participant's housing (table 18)
    - Collect any questionnaires filled in by the participant since the last visit (written texts)

- Complete any missing information of the clinical evaluation (i.e. scanning of a forgotten prescription, scanning of an older written text provided by the participant, write down dictated text)
- Administration of follow up questionnaire (table 17)
- Installation of the currently available FrailSafe system and reminding of the use, the purposes and the technical issues of the FrailSafe material (Session 3.8). Verification of its correct function
- Provide contact details and instructions in case of any help needed
- Set the next appointment to retrieve the FrailSafe material (5th day)

16. Maintenance of the FrailSafe system at home during 3-5 days
17. Daily phone calls during the instauration of the FrailSafe system to catch up with the experience of the use of the material
18. Telephone Follow-up after the second retrieval of the FrailSafe (M30) (table 17)
19. Last clinical evaluation (M33) (tables 5-14)
20. Data collection of written text after the first time (table 16) (M33). The participant will either be helped to provide text by dictation or (s)he will write it down during the clinical assessment appointment
21. Last telephone follow up M36
22. Study's completion verification (table 20). Normally at the end (M36), but could be in anytime in case of premature withdrawal.

Table 20. STUDY'S COMPLETION VERIFICATION

Did the patient complete the study as predicted?	1. Yes 2. No
If no, provide the reason for the premature ending of his/her participation	1. Death 2. Consent withdrawal 3. Emerging condition inhibiting the participation in the study or fulfilling exclusion criteria 4. Participant unreachable/ Lost in follow up

This option will be provided to fill in by the investigator once in each patient's dataset, in the end of his/her participation, whether this corresponds to a completion of the study as predicted or to a premature withdrawal

4.3 Group B- Main group:

1-5. As described above for all groups

6. Complete clinical evaluation session (tables 7, 8, 10, 11, 12, 14) (M10)
7. Data collection regarding social interaction and natural language analysis:
    - Data collection of written text for the first time (table 15), where the participant will either be helped to provide text by dictation or be asked to prepare it him/herself in his/her home and deliver it to us in the next appointment and
    - self-administered questionnaires The Social Media (annex 16) and the Big five (annex 17) questionnaire will be given to participants in order to fill them in themselves and deliver them to us in the next appointment
8. First FrailSafe system home visit (M10):
    - Blood sampling for telomeres
    - Fill in the evaluation form regarding the participant's housing (table 18)
    - Collect any questionnaires filled in by the participant since the last visit: written texts, social media and big five questionnaires
    - Complete any missing information of the clinical evaluation (i.e. scanning of a forgotten prescription, scanning of an older written text provided by the participant, write down dictated text)
    - Installation of the currently available FrailSafe system and explication of the use, the purposes and the technical issues of the FrailSafe material (Session 3.8). Verification of its correct function
    - Provide contact details and instructions in case of any help needed
    - Set the next appointment to retrieve the FrailSafe material (5^{th} day)
9. Maintenance of the FrailSafe system at home during 5 days
10. Daily phone calls during the instauration of the FrailSafe system to catch up with the experience of the use of the material and any problems that may have arisen
11. Short satisfaction interview in the day of FrailSafe system retrieval
12. FrailSafe system home visit (M12)
    - Administration of follow up questionnaire (table 17)
    - Installation of the currently available FrailSafe system and reminding of the use, the purposes and the technical issues of the FrailSafe material. Verification of its correct function
    - Provide contact details and instructions in case of any help needed
    - Set the next appointment to retrieve the FrailSafe material (5^{th} day)
13. Maintenance of the FrailSafe system at home during 3-5 days
14. Daily phone calls during the instauration of the FrailSafe system to catch up with the experience of the use of the material and any problems that may have arisen
15. Short satisfaction interview in the day of FrailSafe system retrieval

16. Repetition of steps 12-15 for a total of 7 FrailSafe system home visits (M12-M27) every 2 months (with the exception of the first three to be conducted in an interval of 3 months (section 2.6).
17. Second clinical evaluation (M16) (tables 5-14)
18. Data collection of written text after the first time (table 16) (M16). The participant will either be helped to provide text by dictation or be asked to prepare it him/herself in his/her home and deliver it to us in the next appointment
19. Third clinical evaluation (M22)
20. Data collection of written text after the first time (table 16) (M22). The participant will either be helped to provide text by dictation or be asked to prepare it him/herself in his/her home and deliver it to us in the next appointment
21. [Only for Patras]: Second blood sampling (M25)
22. Last FrailSafe system home visit (M26). As in steps 12-15 with the addition of:
    - Fill in the evaluation form regarding the participant's housing (table 18)
23. Two telephone follow-ups after the last retrieval of the FrailSafe (M29 andM32) (table 17)
24. Last clinical evaluation (M35) (tables 5-14)
25. Data collection of written text after the first time (table 16) (M35). The participant will either be helped to provide text by dictation or (s)he will write it down during the clinical assessment appointment.
26. Study's completion verification (table 20). Normally at the end (M36), but could be in anytime in case of premature withdrawal.

By following this methodology for groups A and B a considerable amount of continuous data from a large number of participants will be recorded, minimizing the impact of the relatively small number of equipments. It is believed that monitoring these older people, especially of group B, every two months, very little information regarding changes and transition of frailty will be missed. By this time, significant development and many amelioration to the technical aspects of the FrailSafe system is expected to have been achieved.

4.4.1 Group Ci- Standard evaluation group:

1-5. As described above for all groups

6. Complete clinical evaluation session (tables 5, 7, 8, 10, 11, 12, 14) (M31)
7. First FrailSafe system home visit (M31):
    - Blood sampling for telomeres
    - Fill in the evaluation form regarding the participant's housing (table 18)
    - Collect any questionnaires filled in by the participant since the last visit: written texts, social media and big five questionnaires

- Complete any missing information of the clinical evaluation (i.e. scanning of a forgotten prescription, scanning of an older written text provided by the participant, write down dictated text)
- Installation of the currently available FrailSafe system and explication of the use, the purposes and the technical issues of the FrailSafe material. Verification of its correct function
- Provide contact details and instructions in case of any help needed
- Set the next appointment to retrieve the FrailSafe material (5th day)

8. Maintenance of the FrailSafe system at home during 5 days
9. Short satisfaction interview in the day of FrailSafe system retrieval
10. FrailSafe system home visit (M33)
    - Administration of follow up questionnaire (table 17)
    - Installation of the currently available FrailSafe system and reminding of the use, the purposes and the technical issues of the FrailSafe material (Session 3.8). Verification of its correct function
    - Provide contact details and instructions in case of any help needed
    - Set the next appointment to retrieve the FrailSafe material (5th day)
11. Maintenance of the FrailSafe system at home during 5 days
12. Short satisfaction interview in the day of FrailSafe system retrieval
13. Last FrailSafe system home visit (M35). Repetition of steps 12-15.
14. [Only for Patras]: Second blood sampling (M35)
15. Last clinical evaluation (M36) (tables 5-14)
16. Data collection of written text after the first time (table 16) (M36). The participant will either be helped to provide text by dictation or (s)he will write it down during the clinical assessment appointment.
17. Study's completion verification (table 20). Normally at the end (M36), but could be in anytime in case of premature withdrawal.

4.4.2 Group Cii- Long term evaluation group

1-5. As described above for all groups

6. Complete clinical evaluation session (tables 5, 7, 8, 10, 11, 12, 14) (M31)
7. First FrailSafe system home visit (M31):
    - Blood sampling for telomeres
    - Fill in the evaluation form regarding the participant's housing (table 18)
    - Collect any questionnaires filled in by the participant since the last visit: written texts, social media and big five questionnaires
    - Complete any missing information of the clinical evaluation (i.e. scanning of a forgotten prescription, scanning of an older written text provided by the participant, write down dictated text)

- Installation of the currently available FrailSafe system and explication of the use, the purposes and the technical issues of the FrailSafe material (Session 3.8). Verification of its correct function
- Provide contact details and instructions in case of any help needed
- Set the next appointment to retrieve the FrailSafe material (5th day)

8. Maintenance of the FrailSafe system at home during 60 days
9. Short satisfaction interview in the day of FrailSafe system retrieval
10. One follow-up telephone call (M34)(table 17)
11. [Only for Patras]: Second blood sampling (M35)
12. Last clinical evaluation (M36) (tables 5-14)
13. Data collection of written text after the first time (table 16) (M36). The participant will either be helped to provide text by dictation or (s)he will write it down during the clinical assessment appointment.
14. Study's completion verification (table 20). Normally at the end (M36), but could be in anytime in case of premature withdrawal.

4.5 Group D- Control

1-5. As described above for all groups

6. Complete clinical evaluation session (tables 5, 7, 8, 10, 11, 12, 14) (M31)
7. Blood sampling for telomeres (M31)
8. One follow-up telephone call (M33)(table 17)
9. Last clinical evaluation (M36) (tables 5-14)
10. Data collection of written text after the first time (table 16) (M36). The participant will either be helped to provide text by dictation or (s)he will write it down during the clinical assessment appointment.
11. Study's completion verification (table 20). Normally at the end (M36), but could be in anytime in case of premature withdrawal.

5. Architecture of data analysis

5.1 Definition of Frailty Indices

In order to render clinical results measurable, there is a need to define loss of reserve, independently of frailty status as this is defined by Fried's criteria.

On the other hand, FrailSafe Database contains variables at different time points from

- Clinical Evaluation
- Follow up assessment

- FrailSafe system metrics

In this scope, a new combined index (**Combined Frailty index: CoFI**), that will express frailty status relevant to the study's measurements, will be created by adding up two other frailty indices derived from the study, the **Clinical Frailty Index (ClFI)**, corresponding to the results of the clinical evaluation, and the **Technical Frailty Index (TFI)**, corresponding to the metrics derived from the FrailSafe system devices.

Table 21. Frailty Indices definition

ClFI (Clinical Frailty Index): score corresponding to the findings of the clinical evaluation in a time-spot (Appendix I)
TFI (Technical Frailty Index): accumulated score derived from the FrailSafe system metrics during certain time intervals of observation (Appendix II)
Co FI (Combined Frailty index): combined Clinical and Technical frailty score

Each time a programmed clinical evaluation is effectuated, a ClFI score will be calculated, which will be composed by several items that correspond to various aspects of frailty, as they are described by the clinical evaluation sub-questionnaires

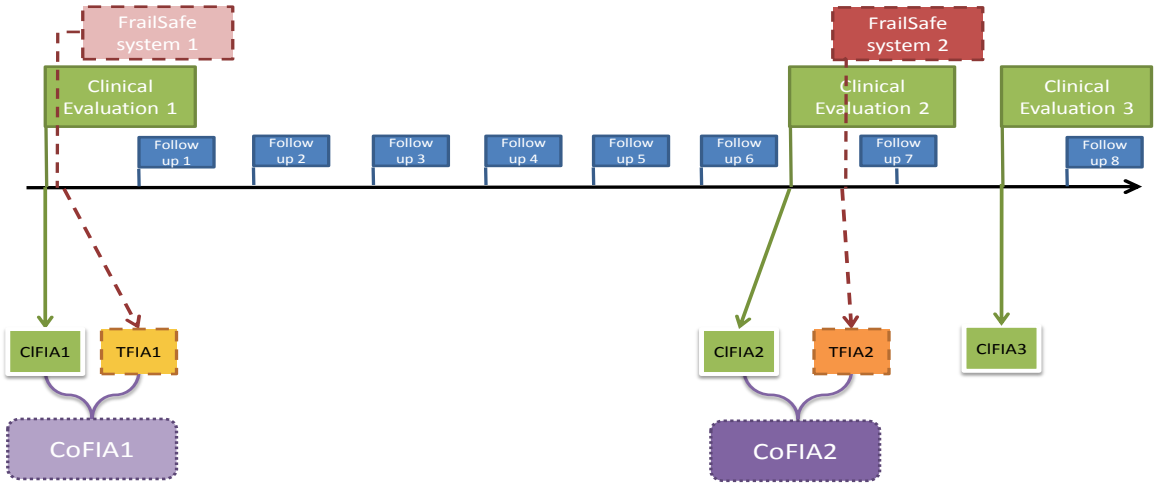


Figure 6. Example of Frailty Indices for a subject belonging to group A.

Similarly, a TFI will be calculated for each FrailSafe system installation, practically, for each FrailSafe home visit. For example, for group A, there will be 2 TFIs calculated, TFIA1 and TFIA2. Similarly for group B there will be 7 TFIs calculated.

Finally, for example for group A, a combined FI, by adding up ClFI and TFI will be calculated twice: CoFIA1=ClFIA1+TFIA1 and CoFIA2=ClFIA2+TFIA2.

5.2 Definition of outcomes

5.2.1 Hard Outcomes

Hard outcome events can be described as significant crude life events that result, because of loss of physiological reserve, in stressful conditions.

Seven main clinical outcomes are defined as hard:

- Fall
- Fracture
- Hospitalisation (non programmed)
- Institutionalisation
- Death
- Decline in ADL or IADL capacity (significant change is defined as decline in at least 1 point in the ADL score and/or 1 point in IADL score)

5.2.2 Proxy outcomes

Due to the limited number of participants, the tight timeframe of the project and the frequency of occurrence of Hard Outcomes, we propose the use of proxy outcomes that we are confident that we will be able to measure and to use in the data analysis part of the project to draw some solid conclusions. The proxy outcomes could also be considered as a diagnostic, early detection tool of a declining condition that may lead to a hard outcome. By keeping a concise, short, practical yet informative track of the change in proxy outcomes we will be able via coaching and interventions to postpone the inevitable occurrence of a Hard outcome, thus improving prognosis and quality of life.

Repeated clinical evaluations are carried out in the following domains: physical, cognitive, psychological, nutritional, and wellness. Loss of function in each domain can indirectly describe loss of physiological reserve, which underscores frailty, and consequently the adverse events of frailty (described above in 5.2.1). The clinical experts of this consortium in a consensus meeting have agreed on a key clinical assessment of each domain, which best describes loss of reserve and is believed to predict adverse outcome.

Therefore, as proxy outcomes have been selected the following:

- Gait speed (Physical Domain)
- MoCA and/or MMSE (Cognitive Domain)
- GDS (Psychological Domain)
- Weight loss (Nutritional Domain)
- Health status self-assessment (General health/Wellness Domain)

The clinicians in the process of selecting a proxy outcome in each domain made use of the bibliography and their expert opinion. At the end of the clinical studies, analysis will be carried out correlating these proxy outcomes to the hard outcomes observed in participants and, if possible, explore validity and reliability.

Review of the bibliography showed that gait speed test has been established as the test with the strongest correlation to frailty (72), and has been linked with the hard outcomes, such as falls and mortality (73,74). Reduced MoCA and MMSE scores, though the later to a lesser extent as less sensitive to the detection of mild cognitive decline, have been linked both with

frailty and adverse outcomes in certain elderly populations (75,76). GDS has been correlated with frailty and may predispose to falls, hospitalization, and increased mortality (77-79). Unintentional weight loss (i.e., more than a 5% reduction in body weight within six to 12 months) is associated with increased morbidity and mortality and may lead to decline of ADL, falls and hip fractures in women (80-82). Self-assessment of health status appears to be a good measure of physical health and risk of death (83,84).

Changes of the measurements of the proxy outcomes will be assessed at regular intervals and at the entry and end of the study interval (according to the study protocol).

The choice of the proxy outcomes has been based on clinical evidence from literature review and clinical practice as described previously. Their contribution and necessity in the Frailsafe project, as well as the mathematical procedures to be applied are described in more details next.

The idea of continuous monitoring with the Frailsafe devices is based on the observation that the physiological decline varies across individuals and that the critical time point to act (e.g. to provide treatment to the older person) follows his/her personalized curve of decline (as shown with red and cyan arrows in the figure below) and does not only depend on the physiological condition at the first evaluation.

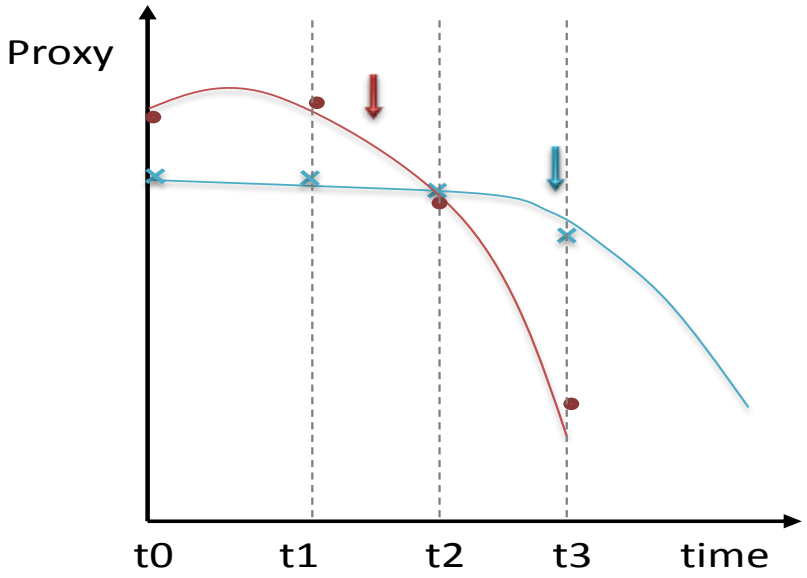


Figure 7. Change of proxy variable f_i over time (measured at 4 time points) for two subjects shown in red and cyan, respectively. The two curves are fitted to the measurements.

Our assumption is that the proxy variables are the main predictors of the hard outcomes but just one time instance is not enough, whereas 1) predicting their values in future instances might help to better estimate adverse events and 2) the incorporation of the variables from the Frailsafe devices might provide additional knowledge that might help to differentiate future states. Therefore the proxy variables will act as the backbone in our predictions, whereas the FS variables will be selected according to their predictive ability and significance.

The first step in our methodology will be to model the temporal change of the proxy variables. We will investigate simple models to represent the temporal variation of the data, such as the quadratic polynomial, for each one of the N proxy variables:

$$f_i(t) = a - b * t - c * t^2, \quad i=1,\ldots, N$$

where a, b and c positive parameters that indicate the starting point and the rate of linear and more rapid (quadratic) change, respectively. Zero values of b and c model the steady state. If less than three time points are available, the estimation of c is not possible and thus will be taken as zero. After completing three clinical evaluations, c can be also estimated.

The second step in the methodology will be to identify the important FS variables as the ones which correlate well with any of the estimated proxy variables f_i. Since an event can have a delayed effect, lag correlations will be also examined to identify possible latencies. If such correlations prove to exist, we will have the means to predict future responses using the FS devices.

Furthermore, in the last step of our methodology when more data become available, statistical (survival) analysis will be performed, using for example the Cox proportional hazards model, in order to find frailty indexes that predict the hard outcomes. This step will have more statistical power when a adequate number of hard outcomes will have happened, thus it will be applied after the 2nd clinical evaluation of group A, as well as by the end of the project. More details on the proposed scores (technical and medical) are provided in Section 5.1 and Appendices I and II.

5.2.3 Other measurable changes

- Difference between the Clinical Frailty Indices
- Difference between the Technical Frailty Indices
- Difference between the Combined Frailty Indices

APPENDIX I- Clinical Frailty Index (ClFI)

We define loss of physiological reserve changes in ten domains investigated by the clinical evaluation assessment (health status, physical performance, nutritional, cognitive, psychological, wellness etc). We add up scores from all variables in order to have an initial rough index that expresses frailty parameters altogether. Due to lack of sufficient data in the literature about the specific weight of each item and even of each domain, we have chosen to initially take equal weights for each item, aiming at validating our model in the end of the study in terms of frailty evolution predictive value, as expressed by outcomes occurrence.

Items that will contribute to the generation of the ClFI are listed in table 22.

Table 22. Components of Clinical Frailty Index

Items	
Medical Domain (M)	Each polypathology /Comorbidities (M)
	Comorbidity's impact (M, P, s, c)
	Polymedication (M, p, c)
	Orthostatic hypotension (M, p)
	Visual impairment (M, S, p)
	Hearing impairment (m, S, c)
General Condition Domain (M, ψ)	Unintentional weight loss (M, ψ)
	Self-reported exhaustion (M, ψ)
Physical Condition (P, m, c)	Balance (single foot standing) (P, m)
	Gait-related task speed* (P, c) (Timed Get Up and Go test)
	Gait - speed 4 m (P, m)
	Lower limb strength (P, m)
	Grip strength –dynamometer (P, m)
	Qualitative evaluation of mobility (P, m)
	Low physical activity (P, M, s, ψ)
Nutrition (M, Ψ, c, s)	Too low BMI (M, Ψ, p, c, s)
	Too high BMI (M, Ψ, P, c, s)
	Waist circumference (M, Ψ, P, c, s)
	Lean body mass (M, P, ψ)
	Total MNA score (M, Ψ, p, c, s)
Cognitive Domain (C, ψ, m, s)	MMSE scores (C, ψ, m)
	MoCA score(C, ψ, m)
	Subjective memory complaint(C, ψ, m, s)
	Natural language analysis (C, Ψ)
Psychological Domain (Ψ, S, c)	GDS-15*(Ψ, S, c)
	Self-rated anxiety (Ψ, S, c)
	Natural language analysis (C, Ψ)
Social Domain (S, Ψ, m)	Living conditions (S, Ψ, p, m)

Social Domain (S, Ψ, m)	Leisure activities (S, Ψ, p, m)
	Membership of a club (S, Ψ, p, m)
	Number of visits and social interactions per week (S, Ψ, p, m)
	Number of telephone calls exchanged per week (S, ψ, m)
	Approximate time spent on phone per week (S, ψ, m)
	Approximate time spent on videoconference per week (S, ψ)
	Number of written messages sent by the participant per week (S, ψ, m, p)
Environmental Domain (S, P, m)	Subjective suitability of the housing environment according to participant's evaluation (S, P, m)
	Subjective suitability of the housing environment according to investigator's evaluation (S, P, m)
	Number of steps to access house (S, P, m)
Wellness (Ψ, S, M, P, c)	Quality of life self-rating (Ψ, S, M, P, c)
	Self-rated health status (M, Ψ)
	Self-assessed change since last year (M, ψ)
	Self-rated anxiety (Ψ, S, M, P, c)
	Self-rated pain (M, P, ψ)
Lifestyle (P, M, ψ,s)	Smoking (M, Ψ, p, s)
	Alcohol (M, Ψ, S)
	Physical Activity (P, M, ψ,s)
Tags (reflecting impact of each item on ClFI)	
Physical: P dominant, p recessive	
Medical: M dominant, m recessive	
Social: S dominant, s recessive	
Cognitive: C dominant, c recessive	
Psychological: Ψ dominant, ψ recessive	

APPENDIX II- Technical Frailty Index (ClFI)

Technical Frailty Index will be constructed according to the fine-tuning of the FrailSafe system that we are going to achieve during the initial period of the field studies (groups A and B). Although its distinct components are going to be evaluated separately, it will be fully used as a composed index in a later phase of the study (experimentation period for group C).

The main components from which it is going to be constructed are presented in general terms in table 23.

Table 23. Components to contribute to the generation of Technical Frailty Index

Measurements	High level data	Frequency
Heart Rate	• Mean value when sitting • Mean value when sleeping • Mean value when walking • Mean value when lying • Mean value when walking upstairs and downstairs	for each day - sampling every 5sec (250 Hz)
Respiration Rate	• Mean value when sitting • Mean value when sleeping • Mean value when walking • Mean value when lying • Mean value when walking upstairs and downstairs	for each day - sampling every 15sec (25 Hz)
Walking	• Number of steps • Number of walking activity initiation • Mean duration of the walking activity	for each day sampling (25 Hz)
Posture	• Mean time spent standing/day • Mean time spent sitting/day • Mean time spent lying/day	for each day
Instability/Falls	• Falls rate • Almost/failed falls rate • Places where falls/almost falls happen (indoors/outdoors) - what type of activity performed • Fall consequences • Physiological state of the subject one minute before • Number of fear of fall instances	for each block
Strength	• Mean max strength value	for each block
Blood Pressure	• Mean value when sitting • Mean value when standing	for each day sampling (3 times)
Game Analysis	• Played the game? • Number of times/block • Success rate • Mean reaction time • Mean Duration • Mean Time of pauses • Number of pauses/block • Events triggered • Concentration index	for each block

Indoor Activities	• Mean time spent sitting in the living room • Mean time spent lying in bed • Mean time spent in the restroom • Mean time spent walking inside • Mean time spent using tablet/pc	for each day
Outdoor Activities	• Mean time spent walking outside • Mean time spent driving car • Mean time spent riding bike • Mean time spent carrying things (e.g. shopping bags)	for each day

5.3 Hypothesis Generation

According to outcomes and Frailty Indices definitions, the medical objectives of the study can be operationally approached as described in table 24.

Table 24. Hypothesis Generation for the analysis of data per MO

MO1.	(Understanding frailty and relation to co-morbidities) What is the relation of most prevalent comorbidities with Clinical Frailty Index and with proxy and hard outcomes.
MO2	(Develop quantitative and qualitative measures to define frailty) Assess the ability of the Technical Frailty Index to describe reduced reserves, as expressed by Clinical Frailty Index and proxy and hard outcomes
MO3	(Use these measures to predict short and long-term outcome) Evaluate the ability of each component of the Clinical or Technical Frailty Indices, and/or combination of those, to predict Proxy and Hard Outcomes
MO4	(Develop real life tools for the assessment of physiological reserve and external challenges) Identify the influence of each component of the Combined Frailty Index to best predict proxy and hard outcomes, in order to validate the predictive value of the Combined Frailty Index.
MO5	(Provide a model sensitive to change) Identify the sensitivity of each component of the Combined Frailty Index to describe shift in reserve as a holistic measure defined by the proxy and hard outcomes
MO6	(Create “prevent-frailty” evidence based recommendations) Assess if positive attitude or changes, that took place in each and every aspect of the frailty sub-indices, contribute to a modification of the expected patterns

	of the proxy and hard outcomes, so as to be proposed as clinical recommendations For example, a recommendation could be provided for physical, cognitive or social actions, which have been tested during the study and have shown a positive profile in regards of proxy and hard outcomes.
MO7	(Achieve all with a safe and acceptable to older people system) Constantly evaluate and record the acceptability and safety aspect of the FrailSafe system application and the totality of the procedures followed during the study.

5.4 Statistics

5.4.1 Handling data with missing values

Our data analysis techniques are capable of dealing with data that are of heterogeneous nature, from multiple devices, modalities, and results of validated questionnaires that are neither normalised nor complete. The algorithms will identify reliable and robust patterns within the data that define shared, homogeneous, rule based categories with common "frailty signatures".

Missing values and measurement noise will be handled by data imputation where prediction is based on unsupervised clustering. We will apply reconstruction of missing parts by applying statistical models learned by available complete data. In particular, data missing from individual subjects and/or sources of information will be estimated based on state-of-the-art techniques and building upon UoP's existing s/w tools. Missing parts will be reconstructed by applying models learned from available complete data borrowing ideas from subspace learning. The most homogeneous clusters with respect to frailty will be detected, and interpretable rules will be extracted from them. Also potential associations with features or categories of interest will be investigated.

In addition to clustering, similarity analysis will be performed. Wavelet and tensor-based decomposition for automatic summarization and concept discovery of high-order datasets by allowing reasoning across all modes of data concurrently (TWave and TWaveCluster) (85) will be used.

The heterogeneous sources of data will be fused either using tensor-based techniques or standard data-mining methods (e.g., kernels, decision trees).

A higher level of information fusion will be applied e.g., ensemble methods that boost the decisions made from different models on individual sources. In such scenarios, data missingness can be handled by emphasizing the importance of data objects with partial

information compared to the common ones. After integrating the heterogeneous data, knowledge discovery on the multidimensional spaces will be performed.

5.4.2 Soundness of conclusions – Sample calculations – Large number of parameters and many ”micro” samples

Our main goal is to explore the relationships of the different parameters measured with the frailty of the older people. A risk appears since the number of parameters is large, the project’s objectives numerous and the participant population limited. As the number of participants cannot be changed, the statistical methodology to be applied is intended to address the dimensionality problem by applying different dimensionality reduction techniques (e.g., step-wise forward feature selection, step-wise backward feature elimination, decision tree induction, principal component analysis,) as well as clustering techniques to partition the data into more homogeneous groups. For example grouping equivalent comorbidities is expected to improve the statistical significance leading to more sound conclusions regarding comorbidities and frailty.

Moreover, correlation analysis can provide us with information on the measure of correlation between two or more parameters. A common measure of correlation or linear relationship between two random variables is the covariance. Another measure of correlation between two random variables, which is often more interpretable is the Pearson correlation, which is an efficient (parametric) statistical indicator to assess whether there is a link between two variables and how to combine them and cluster them in equivalent ones. This way we can perform dimensionality reduction, more efficient exploitation of the clinical trial subject number and obtain increased statistical reliability of the result. The term parametric refers to a series of statistical indicators that meet specific conditions that may be empirical or even laboratory measurements. If these conditions are "missing", one can use non-parametric statistical indicators, which are not affected by compliance or the "violation" of conditions. For the Pearson correlation coefficient, these conditions are: variable representation should be continuous scale of equal intervals that are normally distributed and there is a linear relationship between the two variables to be combined. What is required for the detection of the relationship is to have a proportional relationship between the two variables at all levels. The bigger one can grow over the other one and vice versa. The scattering diagram is a very useful diagram which illustrates the type and (approximately), the size of relationship of the two variables to be clustered together.

5.4.2.1 Ranking the significance of parameters

It is important to investigate the relevance of the data that we include in our parameter dataset, with the values provided by our model. As soon as the model has been established,

it will be assessed in regards to its ability to describe the data that we have. It is important to evaluate and fine tune the significance and contribution of each variable in the model.

To choose the statistically significant variables in a model, we will perform validation tests. These validations will help us investigate what variables do not contribute to the model, and therefore can be removed without loss of information. To investigate the adequacy of our model to describe transitions in frailty, a repertoire of sampling, distribution and statistical functions will be used. To rank the importance of the features or parameters we plan to use the ReliefF algorithm (86, 87). The ReliefF algorithm, which can operate on both discrete and continuous class data, evaluates the worth of an attribute by repeatedly sampling an instance and considering the value of the given attribute for the nearest instance of the same and different class.

For model selection, criteria such as the Bayesian information criterion (BIC) or the Akaike information criterion (AIC), will be used.

5.4.2.2 eFI exploitation

Linking eFI to our dataset will help us exploit the large sample size of the eFI database, which numbers more than 900k+ health electronic records. The eFI uses a 'cumulative deficit' model, which measures frailty on the basis of the accumulation of a range of deficits, which can be clinical signs (e.g. tremor), symptoms (e.g. vision problems), diseases, disabilities and abnormal test values. In total, the eFI is made up of 36 deficits comprising around 2,000 sub-parameters. The score is strongly predictive of adverse outcomes and has been validated in large international studies. We plan to link and associate a subset of our parameters to the eFI parameters at a higher level of abstraction at this stage so that we will be able to evaluate our population using their scoring system. This way, we will be able to strengthen the statistic viability of our study, whilst at the same time being able to assess the added value of the FrailSafe system to our participants.

5.4.2.3 Linking hard outcomes to parameters being measured

Due to the limited number of participants, the tight timeframe of the project and the frequency of occurrence of hard outcomes that can be used as ground truth for our models, we propose the use of significant clinical outcomes, or proxy outcomes, that we are confident that we will be able to measure and to use in the data analysis part of the project to draw solid conclusions. The proxy outcomes could also be considered as a diagnostic, early detection marker of a declining condition that may lead to a hard outcome. In addition to proxy outcomes we measure changes in numerous clinical measurements that comprise the CIFI, continuous quantitative technical measurements via the Frailsafe system that comprise the TFI as well as a combination of both. Through the intensive data analysis (that will include the use of probabilistic models such as Bayesian Networks) we will exploit as

much as possible the small number of hard outcomes and link them to proxy outcomes, the significant clinical outcomes and the more quantitative measures obtained by FrailSafe system to better understand frailty and its relation to comorbidities. In addition, by keeping a concise, short, practical yet informative track of the change (Δ) in proxy outcomes we will be able via coaching and interventions to postpone the inevitable occurrence of a hard outcome, thus improving prognosis and quality of life.

5.4.3 Detecting causality associations among various parameters

We intend to employ Bayesian Networks in order to inference causal relationships among different biosignals and other measurements/assessments of the older people. A BN is a probabilistic graphical model that represents a set of parameters and their probabilistic dependencies (88). In this model, nodes represent parameters of interest, e.g. observations such as high blood pressure, certain manifestation or not of frailty, presence of absence of comorbidities, drugs that have or have not been used, presence or absence of certain symptoms, while arcs encode the conditional dependencies among the variables. Because BNs are complete models for the parameters and their relationships, we will use them to answer probabilistic queries about them. A BN can be either specified by an expert and then used to perform inference, or it can be learned from data (89,90). We plan to use a combined approach and use expert knowledge when possible. To discover causal associations among temporal patterns we propose to use a variation of BNs called dynamic belief networks (DBNs) (91-93). DBNs are temporal models that permit inference across time.

Moreover, we plan to perform causal association studies to the parameters that we investigate in an effort to eliminate duplicate observations, overlaping observations and to achieve a more efficient association of each parameter to the domains under study (e.g. medical, technical, psychological etc).

6. Ethics and Safety

All throughout the study's methodology special care is taken for ethical and safety issues.

The very first step of each participant's recruitment concerns the clear information by both the information letter and the personal interaction with an authorised member of the study. Time is given for answering to questions that may emerge. In the information letter is provided description of the study's procedures, goals, possible benefits and inconveniences, hazard analysis as well as the declaration that the individual can drop out of the study at any time if (s)he wishes it.

In general, the present study does not contain high risk interventions. The installation and use of the FrailSafe system has a monitoring role and potential interventional interactions between the FrailSafe system and the participant are expected to be of no negative effect. Some mechanical hazards (i.e. risk of fall) that may underlie during certain procedures, especially the mobility testing and the virtual or augmented reality experiences when they are applied in a standing position, will be obviated by the attentive presence of a member of the study near the participant.

Material used in the study, essentially the FrailSafe system devices, receive calibration and technical service in the recommended intervals in order to avoid dysfunctions that may carry unforeseen consequences. Special care is given in the respect of the rules of hygiene, especially regarding devices in direct contact with a person's body (WWBS, scale for bioelectrical impedance AR glasses, tensionmeter). Alcoholic solutions are employed for the cleaning of all the instruments before use from the next participant, or equivalent cleaning instructions will be followed.

The WWBS devices are constructed in such a way so as to be washable in the washing machine after the disconnection of certain electronic parts. Moreover, materials and fabrics are also investigated considering functional and fashion aspects but also fully compatibility with body, preferring hypoallergenic and antibacterial materials, to guarantee a safe and prolonged use of the garment. This aspects as well as simplicity of use and easiness to don and doff the system are fundamental for a positive psychological impact on the patient, resulting in higher acceptability and usability of the overall platform. Of course special care to acceptability and tolerance issues will be given regarding all FrailSafe system devices.

The acceptability of the devices to be used by the participant also depends on the fact that no major limitations in the daily activities is expected to rise due to the study. Participants are supposed to continue their personal routine normally and be monitored in their natural environment and activities' framework. Logical adjustments of the study's time programming could be discussed according to the personal program, preferences and participant's availability.

Furthermore, the nature of the study requires the collection, processing, transfer and analysis of a large amount of data. In all these stages, confidentiality and personal data protection will be reassured by an anonymization procedure. Each participant is traced by his/her ID number and only this, and no identifiable personal data, is exposed to large scale data exchange. There will be nowhere a depiction of the participants' faces, no exact date of birth (only the year of birth will be recorded) and in the electronic and paper CRFs only the first two letters of the subject's first and last name will appear, along of course with the ID number. Only specific investigators from each centre will have access to the participants' coordinates' lists and the corresponding files will be kept under circumstances of security. The data collection and persistence will comply with the data protection guidelines reported in deliverable "D9.9: Ethics, Safety and mHealth Barriers" (Section 6) with the aim of, at same time, keeping the maximum level of security and privacy of the data and allowing the

successful performance of the clinical research and of the other tasks of the project. Moreover, data are obtained in accordance to the local ethics requirements. Any personal information regarding the participants is treated as sensitive personal data (as defined in deliverable D9.9) and kept strictly private. Recorded data are anonymized with no personal identifiers and no means to link these to personal identifiers – hence falling outside the scope of legislation concerning personal data.

It is important to notify that during the experimental period of the study the proposed devices are instruments still evolving with sensitivity properties which have not yet been tested. Thus, the FrailSafe system will not aim at taking in charge emergent situations or adverse event which may coincide during the enrolment period, although no undesirable effects are expected to occur due to the FrailSafe system instauration.

However, emergencies, such as a fall or serious arrhythmias, may randomly occur during the study; these emergencies, more specifically, may occur either during the use of the under development FrailSafe system or during the use of the prototype FrailSafe during the evaluation phase.

It is stressed that the FrailSafe team will not be aware of any emergency in real time. During the whole period of the study the analysis of data will be off-line, as a 24hours emergency response service was neither planned nor budgeted. However, the system will include a real time analysis and response, developed in the lab using off-line participants' data; the real time analysis is a feature which will be included, after the end of the project, in the market product.

Except of emergencies, incidental finding may also occur either during the clinical evaluation and follow up or during the use of the FrailSafe system.

a. Incidental findings during clinical evaluation and follow up:

If the researcher during the clinical evaluation finds out medical issues, which according to his/her professional judgment, need to be reported, the guidelines of the protocol on incidental clinical findings will be followed. This protocol will be devised locally in each clinical center, will be put to the attention of the local Ethics Committee, and briefly described in the participant's information sheet. The protocol will state that in case of such events the participant will be informed, and his permission will be sought for his medical practitioner and/or his family and/or carer to be notified.

b. Incidental findings during FrailSafe evaluation

These events are expected to be infrequent, as continuous data will be analysed in batches, and not individually. However, single cases may be needed to be considered individually, and so, such events may still occur. It should be also considered that continuous data will be analyzed off-line at a later stage, definitely after participants having completed the continuous recordings; 5-days recordings for most of the participants and 2-month recordings in the subgroup of the evaluation stage. Thus, incidental events are expected to be historical, though still need to be reported. A similar procedure as in incidental findings during clinical evaluation will be followed.

A protocol on incidental findings during FrailSafe evaluation will be set up locally in each clinical center, will be put to the attention of the local Ethics Committee, and briefly described in the participant's information sheet. The protocol will state that in case of such an event the participant will be informed, and his permission will be sought for his medical practitioner and/or his family and/or carer to be notified.

The participant's permission will be sought, unless this is not applicable due to serious life-threatening condition, which authorizes the investigators to immediately contact regular or emergency health care providers.

An indicative sample of the procedure to be followed (as deposed to the local Authorities in France and will be followed with some adaptations to the other clinical centers also) is presented in Annex **20**.

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8. Annexes

Annex 1- COMORBIDITIES' LIST

(SELF-REPPORTED BY THE PARTICIPANTS AND REVEALED BY THEIR MEDICATION LIST)

COMORBIDITIES	**Check if the condition is present**	**Check if you think that the condition affects significantly the person's functional status**
ARTERIAL HYPERTENSION		
DYSLIPIDEMIA		
DIABETES MELLITUS		
ISCHEMIC HEART DISEASE		
CHRONIC ATRIAL FIBRILLATION/PAROXYSMAL AF OR OTHER ARRYTHMIA		
HEART INSUFFICIENCY		
STROKE OR TIA		
CHRONIC RENAL DISEASE		
RESPIRATORY DISEASE		
CANCER		
IMPAIRED COGNITIVE FUNCTION		
PARKINSON'S DISEASE		
EPILEPSY		
DEPRESSIVE EMOTION		
ANXIETY AND/OR SLEEP PROBLEM		
URINARY INCONTINENCE		
PROSTATE PATHOLOGY		
ANEMIA		
ARTHRALGIES- MUSCULOSCELETAL COMPLAINTS/DISEASES		

OSTEOPOROSIS		
CONSTIPATION AND OTHER INTESTINAL PATHOLOGY		
DYSPEPSY		
THYROID GLAND PATHOLOGY		
EYE DISEASES		
HEARING PROBLEMS		
DIZZINESS AND/OR VERTIGO		
LOWER LIMP TRAUMA OR OPERATION WITH RESIDUAL SIGNES		
OTHER (ICD-10 diagnosis code)		
OTHER (ICD-10 diagnosis code)		
OTHER (ICD-10 diagnosis code)		
OTHER (ICD-10 diagnosis code)		

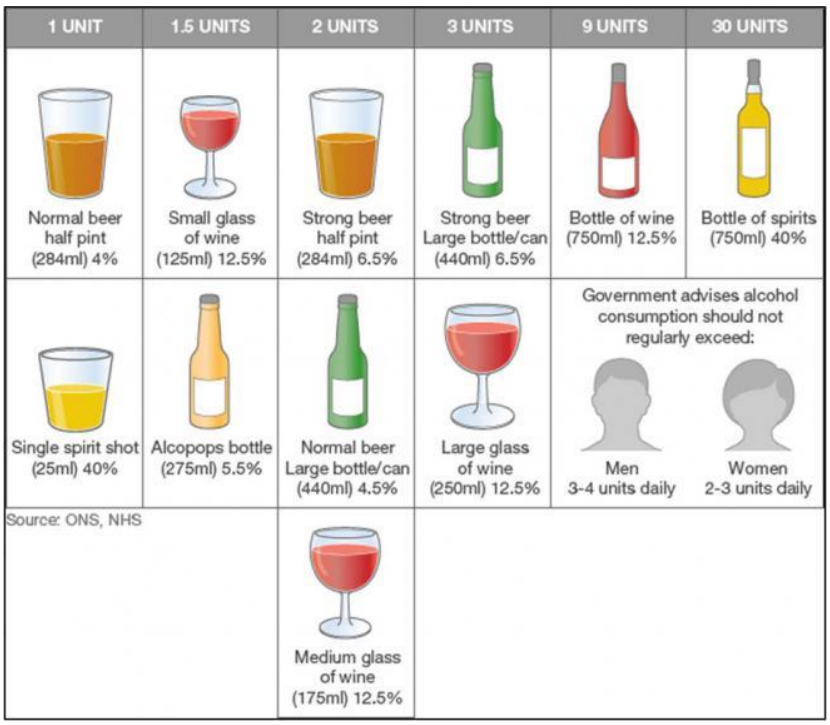
Annex 2: List of lead co-morbidities with special interest for the study:

CONDITION	**Check if the condition is present** **(check all that apply)**	**Check the single condition with the most important impact on this individual's function** (according to clinical evaluation)
Prior stroke		
MCI		
Osteoporosis if woman		
Osteoarthritis of man		
None of the above		

Annex 3- List of medication

ACTIVE SUBSTANCE **(or commercial drug name)**	**Number of administrations per day** (In case of missing information =”I don’t know”, enter the value 999. In case of use as needed (for example when in pain, insomnia etc), enter the value 888 In case of administration frequency regular but lower than once daily, enter the value 777

Annex 4- alcohol units' equivalences



Annex 5- Mini Nutritional Assessment

Mini Nutritional Assessment
MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) = weight in kg / (height in m)²
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score (subtotal max. 14 points) ☐☐
12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished
For a more in-depth assessment, continue with questions G-R

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC greater than 22 ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐
Screening score ☐☐.☐
Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score
24 to 30 points ☐ Normal nutritional status
17 to 23.5 points ☐ At risk of malnutrition
Less than 17 points ☐ Malnourished

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For more information: www.mna-elderly.com

Annex 6- Activities of Daily Living

Index of Independence in Activities of Daily Living (Katz Index of ADL)

Patient's Name:_____ Date:_____

Instructions: For each area of functioning listed below, check the description that applies. (The word "assistance" means supervision, direction, or personal assistance.) Data recorded on the evaluation form is converted into an overall ADL grade with the aid of definitions in the table on the following page.

BATHING – either sponge bath, tub bath, or shower

☐ Receives no assistance (gets in and out of tub by self if tub is usual means of bathing)

☐ Receives assistance in bathing only one part of the body (such as back or a leg)

☐ Receives assistance in bathing more than one part of the body (or not bathed)

DRESSING – gets clothes from closets and drawers – including underclothes, outer garments, and using fasteners (including braces, if worn)

☐ Gets clothes and gets completely dressed without assistance

☐ Gets clothes and gets dressed without assistance except for assistance in tying shoes

☐ Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed

TOILETING – going to the "toilet room" for bowel and urine elimination, cleaning self after elimination, and arranging clothes

☐ Goes to "toilet room," cleans self, and arranges clothes without assistance (may use object for support such as cane, walker, or wheelchair and may manage night bedpan or commode, emptying same in morning)

☐ Receives assistance in going to "toilet room" or in cleaning self or in arranging clothes after elimination or in use of night bedpan or commode

☐ Doesn't go to room termed "toilet" for the elimination process

TRANSFER

☐ Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walker)

☐ Moves in and out of bed or chair with assistance

☐ Doesn't get out of bed

CONTINENCE

☐ Controls urination and bowel movement completely by self

☐ Has occasional "accidents"

☐ Supervision helps keep urine or bowel control, catheter is used, or is incontinent

FEEDING

☐ Feeds self without assistance

☐ Feeds self except for getting assistance in cutting meat or buttering bread

☐ Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids

(Katz et al., 1963)

Annex 7- Instrumental Activities of Daily Living

Instrumental Activities of Daily Living	For each item check the one that applies	Grading
Ability to Use Telephone		
Operates telephone on own initiative; looks up and dials numbers.		1
Dials a few well-known numbers.		1
Answers telephone, but does not dial		1
Does not use telephone at all		0
I do not know		
Shopping		
Takes care of all shopping needs independently		1
Shops independently for small purchases		0
Needs to be accompanied on any shopping trip		0
Completely unable to shop		0
I do not know		
Food Preparation		
Plans, prepares, and serves adequate meals independently		1
Prepares adequate meals if supplied with ingredients		0
Heats and serves prepared meals or prepares meals but does not maintain adequate diet		0
Needs to have meals prepared and served		0
Non applicable-never used to do this		
I do not know		
Housekeeping		
Maintains house alone with occasion assistance (heavy work)		1
Performs light daily tasks such as dishwashing, bed making		1
Performs light daily tasks, but cannot maintain acceptable level of cleanliness		1

Needs help with all home maintenance tasks		1
Does not participate in any housekeeping tasks		0
Non applicable-never used to do this		
I do not know		
Laundry		
Does personal laundry completely.		1
Launders small items, rinses socks, stockings, etc		1
All laundry must be done by others		0
Non applicable-never used to do this		
I do not know		
Mode of Transportation		
Travels independently on public transportation or drives own car		1
Arranges own travel via taxi, but does not otherwise use public transportation		1
Travels on public transportation when assisted or accompanied by another		1
Travel limited to taxi or automobile with assistance of another		0
Does not travel at all		0
I do not know		
Responsibility for Own Medications		
Is responsible for taking medication in correct dosages at correct time		1
Takes responsibility if medication is prepared in advance in separate dosages		0
Is not capable of dispensing own medication		0
Not applicable, does not take any medication		
I do not know		
Ability to Handle Finances		
Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps		1

track of income		
Manages day-to-day purchases, but needs help with banking, major purchases, etc .		1
Incapable of handling money		0
Non applicable-never used to do this		
I do not know		

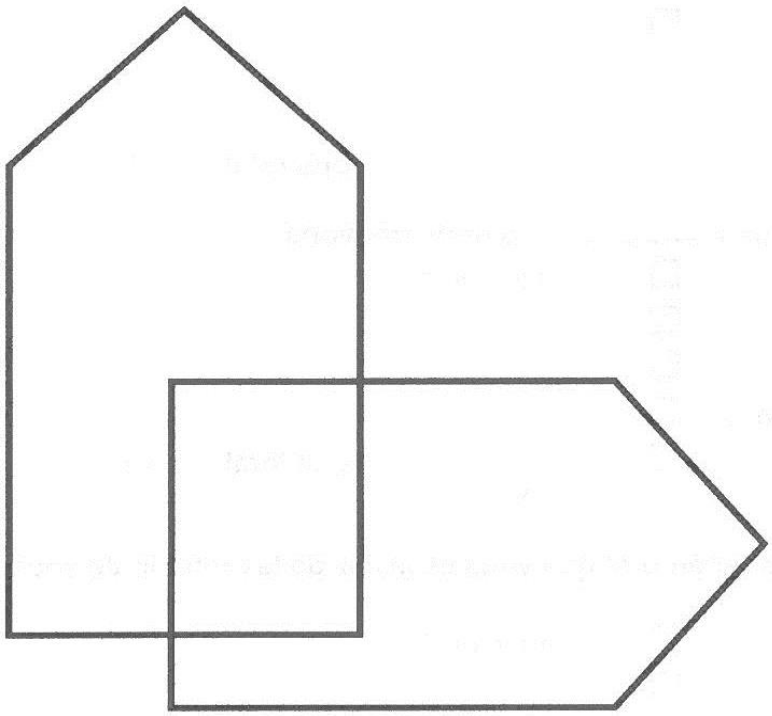
Annex 8a- The Mini Mental State Examination Scale

Folstein Mini-Mental State Exam		
I. **ORIENTATION** (Ask the following questions; correct = ☑)	**Record Each Answer:**	(Maximum Score = 10)
What is today's date?	Date (eg, May 21)	1 ☐
What is today's year?	Year	1 ☐
What is the month?	Month	1 ☐
What day is today?	Day (eg, Monday)	1 ☐
Can you also tell me what season it is?	Season	1 ☐
Can you also tell me the name of this hospital/clinic?	Hospital/Clinic	1 ☐
What floor are we on?	Floor	1 ☐
What city are we in?	City	1 ☐
What county are we in?	County	1 ☐
What state are we in?	State	1 ☐
II. IMMEDIATE RECALL	(correct = ☑)	(Maximum Score = 3)
Ask the subject if you may test his/her memory. Say "ball, "flag," "tree" clearly and slowly, about on second for each. Then ask the subject to repeat them. Check the box at right for each correct response. The first repetition determines the score. If he/she does not repeat all three correctly, keep saying them up to six tries until he/she can repeat them	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐
		NUMBER OF TRIALS: _____
III. **ATTENTION AND CALCULATION**		
A. Counting Backwards Test	(Record each response, correct = ☑)	(Maximum Score = 5)
Ask the subject to begin with 100 and count backwards by 7. Record each response. Check one box at right for each correct response. Any response 7 or less than the previous response is a correct response. The score is the number of correct subtractions. For example, 93, 86, 80, 72, 65 is a score of 4; 93, 86, 78 70, 62, is 2; 92, 87, 78, 70, 65 is 0.	93	1 ☐
	86	1 ☐
	79	1 ☐
	72	1 ☐
	65	1 ☐
IV. **RECALL**	(correct = ☑)	(Maximum Score = 3)
Ask the subject to recall the three words you previously asked him/her to remember. Check the Box at right for each correct response.	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐
V. Language	(correct = ☑)	(Maximum Score = 9)
Naming	Watch	1 ☐
Show the subject a wrist watch and ask him/her what it is. Repeat for a pencil.	Pencil	1 ☐
Repetition		
Ask the subject to repeat "No, ifs, ands, or buts."	Repetition	1 ☐
Three -Stage Command		
Establish the subject's dominant hand. Give the subject a sheet of blank paper and say, "Take the paper in your right/left hand, fold it in half and put it on the floor."	Takes paper in hand	1 ☐
	Folds paper in half	1 ☐
	Puts paper on floor	1 ☐
Reading		
Hold up the card that reads, "Close your eyes." So the subject can see it clearly. Ask him/her to read it and do what it says. Check the box at right only if he/she actually closes his/her eyes.	Closes eyes	1 ☐
Writing		
Give the subject a sheet of blank paper and ask him/her to write a sentence. It is to be written sponataneously. If the sentence contains a subject and a verb, and is sensible, check the box at right. Correct grammar and punctuation are not necessary.	Writes sentence	1 ☐
Copying		
Show the subject the drawing of the intersecting pentagons. Ask him/her to draw the pentagons (about one inch each side) on the paper provided. If ten angles are present and two intersect, check the box at right. Ignore tremor and rotation.	Copies pentagons	1 ☐
DERIVING THE TOTAL SCORE		
Add the number of correct responses. The maximum is 30.		TOTAL SCORE _____

Annex 8b- MMSE item 28

CLOSE YOUR EYES

Annex 8c- MMSE item 30

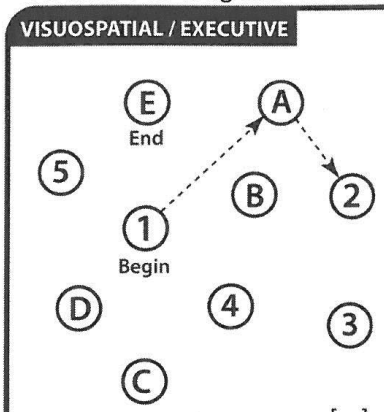


Annex 9- The Montreal Cognitive Assessment Scale

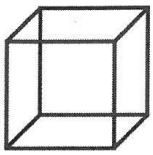
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



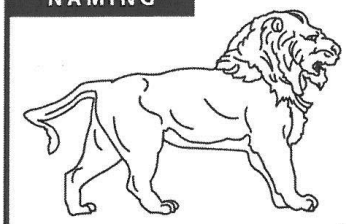
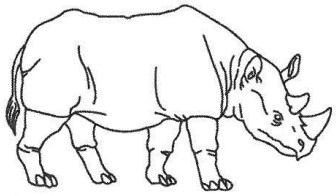
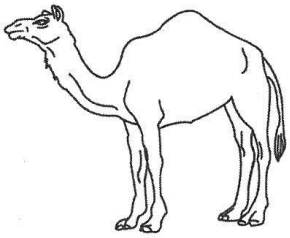
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

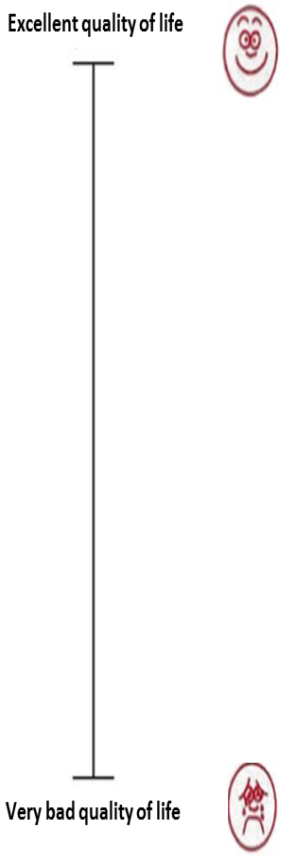
Annex 10: The Geriatric Depression Scale –version 15 items

Choose the best answer for how you have felt over the past week:

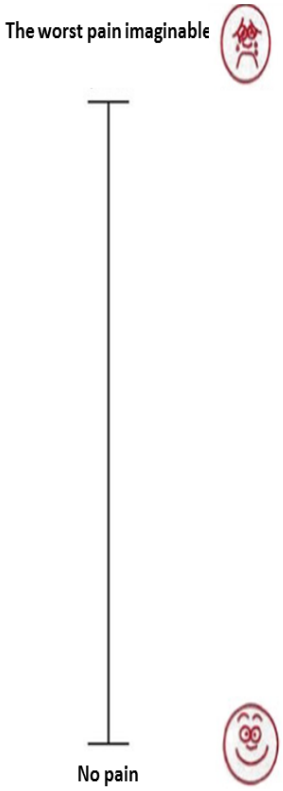
1	Are you basically satisfied with your life?	Yes No	0 1
2	Have you dropped many of your activities and interests?	Yes No	1 0
3	Do you feel that your life is empty?	Yes No	1 0
4	Do you often get bored?	Yes No	1 0
5	Are you in good spirits most of the time?	Yes No	0 1
6	Are you afraid that something bad is going to happen to you?	Yes No	1 0
7	Do you feel happy most of the time?	Yes No	0 1
8	Do you often feel helpless?	Yes No	1 0
9	Do you prefer to stay at home rather than go out and do new things?	Yes No	1 0
10	Do you feel you have more problems with your memory than most?	Yes No	1 0
11	Do you think it is wonderful to be alive now?	Yes No	0 1
12	Do you feel pretty worthless the way you are now?	Yes No	1 0
13	Do you feel full of energy?	Yes No	0 1
14	Do you feel that your situation is hopeless?	Yes No	1 0
15	Do you think that most people are better than you are?	Yes No	1 0

Total score: ……..

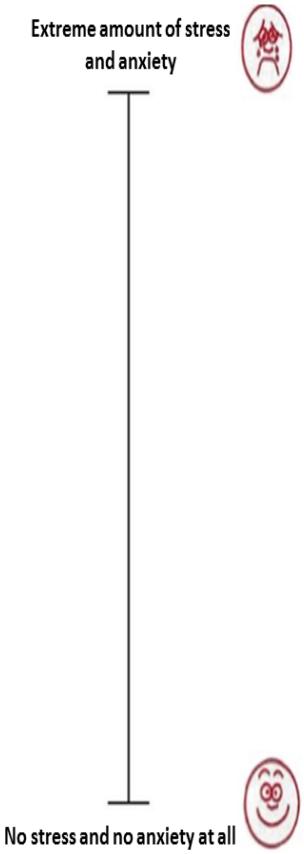
Annex 11- Quality of Life evaluation Visual Analogue Scale



Annex 12- Pain Evaluation Visual Analogue Scale



Annex 13- Anxiety evaluation Visual Analogue Scale



Annex 14- The picture provided for written description

Annex 15- Data collection of written text (self-administration): Form given to the participant to fill in at home in case (s)he is capable of doing so

Dear Mr/Mrs …….

We are very interested in your writings and the way it can alter in time. In order to perform a text analysis we need you to provide us with some written texts, older and current.

1) Please prepare something **that you have written some time ago** to show to our colleague who will visit you at home

2) Please think, a major event of your life or anything else you like. For example you could **describe an enjoyable life** event like:

   A wedding
   Your child's or grandchild's birth
   Some of your personal or your children's achievements
   An enjoyable travel experience
   Professional achievements
   Last time you felt excitement about a forthcoming event.
   Or even an unpleasant even if you like.

   Now please type in a text your thoughts. If it is not possible to type, then write it down by hand. If for any reason you are unable to write, then please, dictate it to our colleague who will visit you at home

3) Please, now type in **what you see in the picture**. If it is not possible to type, then write it down by hand. If for any reason you are unable to write, then please, dictate it to our colleague who will visit you at home

Annex 16- The Social Media Questionnaire

Given to the participant at the end to fill in at his/her home [Leave blank in database all unanswered questions]

Questionnaire for usage of the internet and social media

- This questionnaire is given and answered in a second time
- Administrated once during or after the first clinical assessment

Date administrated: ___/___/_____ (dd/mm/yyyy)

1. **Which means do you use to be kept updated and informed?**
   (more than one answer)

1. Television
2. Newspapers/magazines
3. Family/friends
4. Internet
5. Other……

2. **Do you use the internet?**

[ ] No=1
[ ] Yes =2
If the answer is no, stop here

3. **Do you consider yourself to be familiar internet user ?**
   [ ] beginner =1
   [ ] less familiar =2
   [ ] very familiar=3

4. **Which device do you usually use to connect to the internet?**

(more than one answer)
[ ] Computer/laptop 1=No, 2=Yes
[ ] Tablet 1=No, 2=Yes
[ ] Mobile Phone 1=No, 2=Yes

5. **How often do you connect to the internet per week?**

(the answer can be from 1 up to 7)
[ ] times per week

6. **How many hours per day do you usually use the internet?**

[ ] Hours per day

7. **Which internet services do you usually use?**

(more than one answer)
[ ] News/ Update/Information 1=No, 2=Yes
[ ] Communication, Social media 1=No, 2=Yes
[ ] Entertainment (games, music, TV, video) 1=No, 2=Yes
[ ] Online Transactions 1=No, 2=Yes
[ ] Other: .....

8. **Describe in a few words your 'internet' activity and the changes it has have brought upon your life**

.....
.....
.....
.....

9. **Do you use any social media (i.e. facebook etc)?**

[ ] No, I have never used them
[ ] No, i do not use them but i used to =1
[ ] Yes I use the social media =2
Why did you stop; ……

If the answer is no, then stop here. Otherwise, continue further.

10. **How long have you been using social media?**

I have used social media for [ ] months

11. **Which of the social media below do you use?**

(more than one answer)

[ ] Facebook 1=No, 2=Yes
[ ] Twitter 1=No, 2=Yes
[ ] YouTube 1=No, 2=Yes
[ ] Instagram 1=No, 2=Yes
[ ] Personal blog 1=No, 2=Yes
[ ] Other: .....

12. **How often do you use social media per week?**

(the answer can be 1 up to 7)
[ ] times per week

13. **When you use social media, how many hours per day do you usually use them for?**

[ ] hours per day

14. **What made you use social media for the first time?**

.....
.....
.....
.....

15. **Do you think that social media are easy to use?**

[ ] Very easy =1
[ ] Easy =2
[ ] Difficult =3
[ ] very difficult =4

16. **Do you consider yourself a familiar user of social media ?**

[ ] Beginner =1

[ ] Less familiar =2

[ ] Very familiar =3

17. Which of the above information is included in your profile?

(more than one answer)
[ ] Real name 1=No, 2=Yes
[ ] e-mail 1=No, 2=Yes
[ ] telephone 1=No, 2=Yes
[ ] House Location 1=No, 2=Yes
[ ] Photographs 1=No, 2=Yes
[ ] Video 1=No, 2=Yes
[ ] Religion 1=No, 2=Yes
[ ] Interests 1=No, 2=Yes
[ ] Other:.....

18. Does the information you provide on social medial represent reality and why?

[ ] No =1

[ ] Yes=2

Why:

.....

.....

19. Fill in only if you use twitter, or otherwise go to question 22

How many followers you have on twitter?

[ ] (fill in a number)

20. How many people do you follow on twitter?

[ ] (fill in a number)

21. How often do you tweet per week?

[ ] (fill in a number)

22. How many friends/contacts do you have on facebook?

[ ](complete number) (Fill in only if you use facebook, otherwise go to question 24)

23. How many of your Facebook friends do you consider your true friends from all your friends/contacts?

[ ] Only a few =1
[ ] many of them =3
[ ] most of them =4
[ ] everyone=5

24. Do you accept friend requests from strangers at your social media accounts?

[ ] never =1
[ ] sometimes =2
[ ] always =3

25. What do you usually do during your social media visits?

(Fill in with numbers by beginning with 1 from the most frequent to the least frequent activity)
[ ] post
[ ] share
[ ] like
[ ] comment
[ ] share a photo
[ ] share a link
[ ] share video/music
[ ] other:.....

26. Do you follow politicians/organizations on social media?

[ ] No =1
[ ] Yes=2

27. Do you believe that communication between politicians and voters through social media is important?

[ ] Strongly agree=1
[ ] Agree=2
[ ] Disagree=3
[ ] Strongly disagree=4

28. What type of pages you follow at social media?

.....
.....

29. Do you believe that social media affect your social life

[ ] very positively =1
[ ] positively =2
[ ] Do not affect at all =3
[ ] Negatively =4
[ ] Very negatively =5

30. Besides the activity of yourself and of your contacts, is there anything else that draws your attention in social media? (i.e. Advertisements, offers etc)? How do you respond to this? Does it affect your judgment in some degree?

.....
.....
.....

31. Do you think that there is a danger for the safety of your personal data in social media?

[ ] Strongly agree =1

[ ] agree=2
[ ] disagree=3
[ ] strongly disagree =4
[ ] I don't know/doesn't concern me=5

32. Do you believe that the privacy policies of the social media that you are using are effective?

[ ] Strongly agree=1
[ ] I agree=2
[ ] I don't know/it doesn't concern me=3

33. Are you aware of who can check your profile and the information it contains in the social media you are using?

[ ] No=1
[ ] yes=2
[ ] I don't know / it doesn't concern me=3

34. Have you changed your security settings in social media in order to protect your personal data?

[ ] No=1
[ ] Yes=2

Annex 17- The Big five questionnaire

In order to be recognized the traits Big Five model each person should answer in the following Likert scale a questionnaire which includes 44 questions.

Strongly Disagree → 1
Disagree a little → 2
Neither agree nor disagree → 3
Agree a little → 4
Strongly Agree → 5

The questions are the following:

I see myself as someone who …

___1. Is talkative

___2. Tends to find fault with others

___3. Does a thorough job

___4. Is depressed, blue

___5. Is original, comes up with new ideas

___6. Is reserved

___7. Is helpful and unselfish with others

___8. Can be somewhat careless

___9. Is relaxed, handles stress well

___10. Is curious about many different things

___11. Is full of energy

___12. Starts quarrels with others

___13. Is a reliable worker

___14. Can be tense

___15. Is ingenious, a deep thinker

___16. Generates a lot of enthusiasm

___17. Has a forgiving nature

___18. Tends to be disorganized

___19. Worries a lot

___20. Has an active imagination

___21. Tends to be quiet

___22. Is generally trusting

___23. Tends to be lazy

___24. Is emotionally stable, not easily upset

___25. Is inventive

___26. Has an assertive personality

___27. Can be cold and aloof

___28. Perseveres until the task is finished

___29. Can be moody

___30. Values artistic, aesthetic experiences

___31. Is sometimes shy, inhibited

___32. Is considerate and kind to almost everyone

___33. Does things efficiently

___34. Remains calm in tense situations

___35. Prefers work that is routine

___36. Is outgoing, sociable

___37. Is sometimes rude to others

___38. Makes plans and follows through with them

___39. Gets nervous easily

___40. Likes to reflect, play with ideas

___41. Has few artistic interests

___42. Likes to cooperate with others

___43. Is easily distracted

___44. Is sophisticated in art, music, or literature

Annex 18- Form of traceability of blood sampling destined to telomeres analysis

Sensing and predictive treatment of frailty and associated co-morbidities using advanced personalized models and advanced interventions

Principal Investigator: ……..

ID : ……
Laboratory examination: **Measurement of telomeres' length**
Date of blood sampling: ……..
Prescriber physician: ……..

Drawn on …… at …..…… (time)
Put in deep freezer (-80°C) on …… at ……(time)
Person who draws the sample :……..
Function: (nurse/ laboratory technician/ physician)

- ☐ Patient's consent given
- ☐ EDTA tube
- ☐ Conservation at 4°C during the transport
- ☐ Time limit until freezer respected (3 hours max)

Comments :

Copy for the laboratory

Sensing and predictive treatment of frailty and associated co-morbidities using advanced personalized models and advanced interventions

Principal Investigator :……

ID : ……
Laboratory examination: **Measurement of telomeres' length**
Date of blood sampling: ……..
Prescriber physician: ……..

Drawn on …… at …..…… (time)
Put in deep freezer (-80°C) on …… at ……(time)
Person who draws the sample :……..
Function: (nurse/ laboratory technician/ physician)

- ☐ Patient's consent given
- ☐ EDTA tube
- ☐ Conservation at 4°C during the transport
- ☐ Time limit until freezer respected (3 hours max)

Comments :

Copy to be stored in the patient's folder

Annex 19- Operational procedures' check lists

A. Clinical Evaluation Visit

The participant should be asked to bring:

- ✓ A medication prescription or the boxes of the medication they take
- ✓ Samples of older written texts they produced
- ✓ Their glasses and/or their hearing aid
- ✓ Comfortable shoes
- ✓ Their walking aid if there is one

The investigator should make sure that the "clinical evaluation visit kit" contains:

- ✓ Papers/ questionnaires/ consent forms
- ✓ Pens
- ✓ Pencil (for the MMSE)
- ✓ Watch (for the MMSE)
- ✓ Measure tape (for body circumferences measurements and the definition of the 3 meter distances for the gait tests)
- ✓ Electronic scale
- ✓ Stopwatch (for gait tests)
- ✓ Electronic tensionmeter
- ✓ Mobilograph
- ✓ Tablet(with internet connection)+ charger
- ✓ Dynamometer + batteries
- ✓ Ruler (to quantify the VAS)
- ✓ IMUs

B. The FrailSafe session home visit

The nurse should make sure that for each visit the "FS home suitcase" contains:

- ✓ Her own smartphone
- ✓ The smartphone for the participant +charger
- ✓ Some phone cases in order the participant to choose which one suits him/her best
- ✓ The WWS device (straps): if should be cleaned +charger
- ✓ The tablet +charger
- ✓ The dynamometer
- ✓ The tensionmeter
- ✓ The beacons
- ✓ The AR glasses
- ✓ The plug adaptors needed for some devices (WWS electronic box, smartphones etc)
- ✓ The power strip for multiple plug charging

- ✓ Batteries
- ✓ Measure tape (in case some gait tests are required)
- ✓ Stopwatch (in case some gait tests are required)
- ✓ Paper/pen material in case of written text dictation
- ✓ Blood sampling material (only for the first visit)
- ✓ Any educational and informative material each center prepares to facilitate the education of the participants in the use of the FS system material
- ✓ The housing evaluation questionnaire and phone follow up questionnaires in paper form
- ✓ Disinfecting product to clean up the devices if needed

Note: in case of more than one FS home visits per day, this material should be multiplied accordingly

Tasks and actions in practice:

Before the visit

- ✓ Contact the participant and fix the appointment for the FS visit
- ✓ Verify that all required material are available and ready for use

During the installation visit

- ✓ Blood sample (only first visit)

- ✓ Explication of the use, the purposes and the technical issues of the FrailSafe material: educate the participants and check their comprehension

    - WWS:
        i. Put on-put off demonstration
        ii. Instructions for the recommended use and duration
    - BP device
        i. Explication of the conditions of BP measurements
    - Tablet
        i. Demonstration of the virtual games
    - Dynamometer
        i. Demonstration of the game
    - Smartphone + phone case
        i. Explication of the importance of carrying around the smartphone as continuously as possible
    - AR glasses
        i. tests performed during the nurse's presence
        ii. demonstration of games to play on their own
    - Beacons
        i. Installation in rooms
        ii. Verification of their connectivity to the smart phone

iii. Write down the coordinates of the placement

- ✓ Education on the charging of the various material + provide with some extra batteries
- ✓ Provide the participant with written instructions about the use the material and with contact details in case its needed
- ✓ Collect any questionnaires filled in by the participant since the last visit, ex written texts, social media questionnaires or help him/her write the text
- ✓ Fill in the "phone" follow up questionnaire
- ✓ Fill in the questionnaire regarding the participant's housing
- ✓ Complete any missing information of the clinical evaluation ex prescription photo, older written text photo
- ✓ Before leaving verify the connectivity and the well-functioning of all material
- ✓ Set the next appointment to retrieve the FS material (5^{th} day)

During the session period

- ✓ Telephone Follow-up **during** the instauration of the FS system in an everyday basis to catch up with the experience of the use of the material
- ✓ On call availability to resolve any issues
- ✓ Possibility for additional visits between the installation and the retrieval if needed

During the material retrieval visit

- ✓ Retrieval of all material left at the participant's house
- ✓ Satisfaction questionnaire

After the session

- ✓ Upload total trial data from all measurements (internet needed).
- ✓ Restore and clean all material used

Annex 20- Undesirable event's declaration forms and procedures

ADVERSE EVENT FORM

Principal investigator: _____

Participant's ID number: ⌴⌴⌴⌴ Participant's initials: ⌴⌴_⌴⌴

Event description

(please use one form for each event)

Description or name of event	
Date of event's onset	⌴⌴/⌴⌴/⌴⌴⌴⌴ ☐ Unknown
Date of resolution	⌴⌴/⌴⌴/⌴⌴⌴⌴ ☐ Unknown
Intensity (only one answer possible) *In case of serious or secondarily serious adverse event, also fill in the SERIOUS ADVERSE EVENT FORM*	☐ Mild ☐ Moderate ☐ Serious since appearance ☐ Secondarily Serious
Relationship to FrailSafe device (only one answer possible)	☐ probably related ☐ possibly related ☐ not related
Anticipated	☐ Yes ☐ No
Management	
Evolution	☐ Recovered without aftereffect ☐ Recovered with aftereffect: _____ ☐ Subject not recovered yet ☐ unknown
Comments	

Date of event declaration: ⌴⌴/⌴⌴/⌴⌴⌴⌴

Declaring person and signature:

SERIOUS ADVERSE EVENT FORM

to fax in the next 24(working) hours following the event to the monitoring authority:
Monitoring authority (Sponsor) _____

Principal investigator: _____

Participant's ID number: ␣␣␣␣ Participant's initials: ␣␣_␣␣

Event description

(please use one form for each event)

Description or name of event	
Date of event's onset	␣␣/␣␣/␣␣␣␣ ☐ Unknown
Date of resolution	␣␣/␣␣/␣␣␣␣ ☐ Unknown
Intensity (only one answer possible)	☐ Serious since appearance ☐ Secondarily serious
Relationship to FrailSafe device (only one answer possible)	☐ probably related ☐ possibly related ☐ not related
Seriousness (more than one answers possible)	☐ Hospitalization ☐ Institutionalization ☐ Potential disability ☐ Life threatening ☐ Death; date of death: ␣␣/␣␣/␣␣␣␣ ☐ Other……
Anticipated	☐ Yes ☐ No
Management	
Evolution	☐ Recovered without aftereffect ☐ Recovered with aftereffect: _____ ☐ Subject not recovered yet ☐ unknown
Comments	

Date of event declaration: ␣␣/␣␣/␣␣␣␣
Declaring person and signature: