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2.4.1	11/6/17	Draft	Marina Kotsani (INSERM) Konstantinos Deltouzos (UoP)	First Draft
2.4.2	14/6/17	Draft	Athanase Benetos (INSERM)	Several Revisions
2.4.3	27/6/17	Draft	Dimitrios Vlachakis (UoP) Eva Zacharaki (UoP)	Contribution to a session's writing
2.4.4	27/6/17	Final	Marina Kotsani (INSERM) Athanase Benetos (INSERM)	Contributions' integration and final corrections

EXECUTIVE SUMMARY

The present report constitutes the preliminary version of the deliverable D2.4 Completion of quantification campaign, which reports the specific tests targeted to the quantification and the optimization of the FrailSafe framework.

This deliverable is related to task 2.2 Clinical monitoring of older people, in the context of which participants of the study are followed up for a period of time and monitored for their frailty level and its transition, by several clinical and technological means. Data collected during this follow up are integrated into the FrailSafe system framework, build up a clinically annotated database of divers variables and can be used to more precisely and early quantify frailty aspects, identify risk profiles, construct prediction models and quantify and fine-tune the intervention services that will be developed in WP5. Collected data will be analysed with several tools such as cluster, spectral and factor analysis, so as to reveal indicators that are descriptive of frailty triggering events and risk assessment models.

The first part of this report is an introduction describing the theoretical concept of the added value that FrailSafe integrated system is expected to add upon the classical clinical approach employed so far for the quantification of frailty.

In the first main section of the report, clinical metrics are described under the prism of their operational function to quantify frailty, also taking under consideration the interrelationships that run through the implication of each variable in the various aspects of frailty. The following section describes, in a similar way, the technical metrics and their potential translation into clinically meaningful measurements, also implying their multi-aspect implication through the frailty range.

This integration and interaction between various frailty metrics is terms of conceptualisation and of data analysis process is described in the last two sessions of this report.

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/		
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Work package number:	2	**Title:**	Clinical studies, measurements, clinical analysis

Date of delivery	**Contractual**	**30/06/2017 (M18)**	**Actual**	30/06/2017
Status	Draft ☐		Final ☒	
Nature	Report ☒	Demonstrator ☐	Other ☒ (data)	
Dissemination Level	Public ☒	Consortium ☐		
Abstract (for dissemination)	The deliverable reports on the clinical and technical metrics that are employed for the quantification of various frailty aspects, their interrelationship and their integration process into the FrailSafe system framework in order to develop frailty biomarkers, prediction models and eventually preventive strategies in the stage of the final integrated FrailSafe product.			
Keywords	Quantification, clinical metrics, technical metrics, integration process, interrelationship between variables, aspects of frailty, system fine-tunning, system calibration, validation, prediction, biomarkers.			

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List of abbreviations and acronyms

(*in alphabetic order*)

BMI	Body Mass Index
CGA	Comprehensive Geriatric Assessement
GDS-15	Geriatric Depression Scale 15 items
GPS	Global Positioning System
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MNA	Mini Nutritionnel Assessment
MoCA	Montreal Cognitive Assessment
TUG	Timed get Up and Go test
VPM	Virtual Patient Model
VSM	Virtual Super Market
WP	Work Package
WWBS	Wearable WBAN System
WWS	Wearable Wellness System

1. Introduction

One of the main purposes of this project is to identify and propose new frailty metrics. For operational and methodological reasons since the begging of the study the Fried’s classification of frailty status has been employed (1). Still, the objectives of the study go beyond the detection of the predictive value and the description of the evolution of the frailty status according to Fried’s phenotype. They rather aspire to construct, fine-tune and optimise a combined frailty metric and prediction model, integrating data obtained by various resources.

On the one hand, these resources refer to classical evaluations and measurements conducted into the framework of Comprehensive Geriatric Assessment (CGA). This source of information, even though widely recognized and highly appreciated as the gold standard method to evaluate frailty aspects in a comprehensive and reliable way, it also bears some restrictions and inherent drawbacks (Figure 1).

Firstly, it is conducted in medicalised settings, outside the environment where the person actually lives, functions and interacts with his or her surroundings. By conducting non-ecological evaluations, many valuable elements, mostly those regarding behavioral monitoring and everyday functioning, could pass by unnoticed.

Secondly CGA is conducted in a single time shot, which can be neither representative of the overall situation meant to be tested, nor able to detect slight changes encountered over short periods of time between scheduled evaluations, which are usually less frequent.

Thirdly, the amount of information able to be collected during a CGA session is limited and prone to collection and recall biases and subjective interpretations.

A last aspect that should be added to the inconveniences of using CGA, as the main single tool for evaluating frailty, is its requirement of a considerable time and expertise (2,3). A typical CGA is usually conducted at specialised geriatric centres, by highly trained health professionals, often of divers specialties, in a timeframe that rarely requires less than 2 hours. Therefore, scarce resources’ management creates accessibility difficulties for a substantial proportion of the geriatric population. Even individuals who are believed to benefit from it, like persons with early frailty signs (4,5), are supposed to be referred to GCA, after being selected by rapid scanning procedures from the primary care settings (2,6–8).

Almost contradictory to the idea of reliable early screening of high risk profiles is the fact that in order to identify the persons who will most likely benefit from early interventions, we employ rapidly administered but not always sensitive enough tools, often lacking the opportunity of early detection of mild subclinical phenotypes.

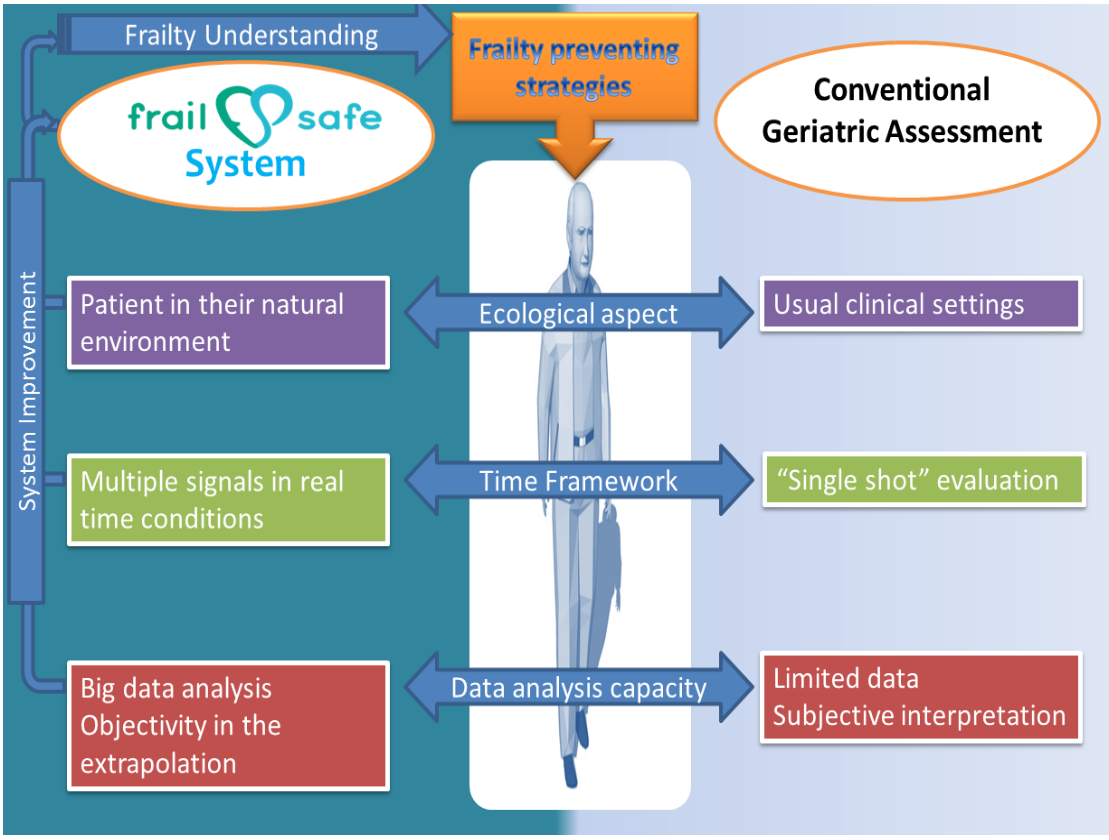


Figure 1. The concept of the presumed added value of the FrailSafe system on the top of the conventional geriatric assessment. Comparison of the characteristics of the two assessment methods in terms of the ecological aspect, the time framework and the data analysis capacity.

Additionally to frailty detection possibilities, classical interventional approaches are equally limited by the aforementioned restrains. Health life style recommendations and the implementation of rehabilitation programs (usually proposed to groups) (9,10) are limited by their low adherence and accessibility and frequency issues accordingly.

The FrailSafe framework aims to surpass these disadvantages by proposing a novel model of health care delivery (Figure 1).

The integrated FrailSafe approach proposes an ecological, real-time, large scale monitoring system, where multiple objective data are available for analysis, virtual patient modelling, algorithmic processing, individualised profile determination, and tailored interventional propositions. The latter could be a personalised guidance program delivered by technological means in an adjustable frequency and intensity, fine-tuned by the very system's feedback loop.

However, before reaching its ultimate goal as a complete early diagnosis and intervention system, the FrailSafe framework has to be tested and validated for its detection and prognostic properties. The study's first phase, during which multiple data are collected and processed, aims at evaluating and validating the added value of the new technological approach the FrailSafe system provides on the top of the classical CGA, towards early detection and transition of frailty stages.

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

The FrailSafe integrated database collects variables' measurements at different time points from multiple sources such as

- Clinical Evaluation visits' metrics and clinical follow up assessments
- FrailSafe system devices' metrics.

2. Clinical metrics

Clinical evaluation assesses eleven domains of the general health and well-being status of a person and investigates the multiple aspects of frailty, beyond classical frailty operational definitions. These domains are: medical health status, general condition, lifestyle habits, physical performance, nutritional condition, cognitive performance, psychological situation, social context, materialistic environmental context and self-assessment of wellness.

Table 1 summarizes the domains assessed during the clinical evaluation sessions and the items composing each domain. Descriptive statistics from the measurements conducted so far, are provided in Deliverable 2.6 Behavioral Monitoring (M18).

Of course, in terms of study of biological variables, even more when dealing with complex clinical situations and real-life individuals, the strict distinction of each domain is impossible and not even desirable in the process of creating a highly performing new frailty metric. For this reason, a tagging system has been employed in order to express the inter-domain interaction of the several studied parameters and the various aspects of frailty each one could depict. These tags refer to the impact of each item on the construction of the Clinical Frailty Index, described in the revised version of Deliverable 2.1 Clinical Study Methodology (M12). They consist of the labelling of the items with major or minor indicators:

- M refers to a major impact on or relation to the medical domain (dominant), whilst m to a more modest one (recessive);
- P refers to a major impact on or relation to the physical and fuctional domain (dominant), whilst p to a more modest one (recessive);
- S refers to a major impact on or relation to the social domain (dominant), whilst s to a more modest one (recessive);
- C refers to a major impact on or relation to the cognitive domain (dominant), whilst c to a more modest one (recessive);
- Ψ refers to a major impact on or relation to the psychological domain (dominant), whilst ψ to a more modest one (recessive);

Table 1. Clinical metrics. Domains investigated by the clinical evaluation.

Items	
Medical Domain (M)	Number of Comorbidities (M)
	Comorbidity's impact (M, P, s, ψ)
	Polymedication (M, p, c)
	Hospitalisations (M)
	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, p, ψ)
Lifestyle domain (P, M, ψ,s)	Smoking (M, ψ, p, s)
	Alcohol (M, Ψ, S)
	Physical Activity (P, M, ψ, s)
Functional capacity domain (M, P, s, c, Ψ)	Basic Activities of Daily living (M, P, s, c, Ψ)
	Instrumental Activities of Daily Living (M, P, s, c, 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)
	Low physical activity (P, M, s, ψ)
	Falls (P, m, Ψ)
	Fractures (P, M)
Nutritionnal domain (M, Ψ, c, s)	Too low BMI (M, Ψ, p, c, s)
	Too high BMI (M, Ψ, P, c, s)
	High waist circumference (M, Ψ, P, c, s)
	Lean body mass (M, P, ψ)
	MNA screening and total (when applicable) 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)
	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)
	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 (P, S, m)
Wellness domain (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)
Tags (reflecting impact of each item on each of the aspects of frailty) Physical/functional: P dominant, p recessive Medical: M dominant, m recessive Social: S dominant, s recessive Cognitive: C dominant, c recessive Psychological: Ψ dominant, ψ recessive	
Abbreviations: BMI: Body Mass Index, GDS-15: Geriatric Depression Scale 15 items, MMSE: Mini Mental State Examination, MNA: Mini Nutritional Assessment, MoCA: Montreal Cognitive Assessment.	

Detailed description of the items involved in the evaluation of each domain, the rational supporting the choice of their measuring methods and scales, their grading system, as well as the annexes of the actual questionnaires and operational procedures followed for the collection of all these data, are described in detail in the Deliverable 2.1 Clinical Study Methodology (M6, revised M12).

Below it is explained the operational treatment of each variable (continuous, dichotomous or ordinal), presented by the domains they belong to, but also referring to the inter-domain interactions and possible correlations that each and every one variable could have with several frailty aspects.

2.1 Medical domain

The items that are evaluated in the medical domain are:
- the number of co-existing chronic conditions (continuous variable), indirectly reflecting the burden of chronic comorbidities in quantification means and mainly representing the medical aspect of frailty(11–13).
- The number of comorbidities with a significant impact over a person's functional status (continuous variable), according to the clinicians' estimation. This item, apart from its medical aspect, also touches a dominant physical aspect and has more discreet social and psychological implications, since it bears also a quantitative evaluation of the burden of a disease.
-The number of active substances taken per day (continuous variable), touching the aspects of mainly the medical domain, but also the physical and cognitive one, since polypharmacy is regularly related to secondary effects on physical and cognitive function (fall risk augmentation, negative cognitive pharmacological actions etc). Polypharmacy is typically considered a frailty criterion itself by many frailty screening tools (14–17). Moreover, it raises the risk of iatrogenic adverse events, a condition conserving especially frail older individuals (14,16,18,19)
- The number of hospitalizations in the last year and in the last three years (continuous variable). This item, predominantly belonging to the medical domain of frailty, could give an indirect quantitative index of a person's health status, and its evolution in the last three years, adding a dynamic aspect in frailty evaluation.
- the presence of orthostatic hypotension (dichotomous variable), reflects medical and secondarily physical/functional frailty and often predisposes to adverse clinical outcomes such as falls, fatigue and activity restriction (20).
- Visual impairment (ordinal variable), often related to chronic medical conditions, can also contribute to social and physical/functional restrictions.
- Hearing impairment (ordinal variable), related to the medical domain, mainly contributes to the social aspect of frailty. It also has implications to the cognitive function.

2.2 General condition domain

The items that are evaluated in the general condition domain are:
- the unintentional weight loss (dichotomous variable), an element with medical and potential psychological aspects, associated with raised risk of mortality and also one of the criteria of Fried's operational frailty definition (1,21,22).
- The self-reported exhaustion (dichotomous variable), a symptom with potential medical implications, but often touching also the psychological domain in terms of origins and the physical/functional domain in terms of consequences. This item also consists another classical Fried's frailty definition criterion (1,23).

2.3 Lifestyle domain

The items that are evaluated in the lifestyle domain are:
- the smoking status (ordinal variable), reflecting mostly medical, but also psychological, physical and social aspects of frailty, cannot be missed once evaluating a person's overall health condition.
- The alcohol intake (continuous variable), similarly to the smoking status, completes the profile of the global clinical evaluation.
- The amount of physical activity regularly conducted (ordinal variable) reveals aspects of physical/functional condition, medical condition profile, with psychological and social dimensions(24–29).

2.4 Functional capacity domain

The items that are evaluated in the functional capacity domain are closely related to the level of autonomy, core concept in the frailty evaluation:
Capacity in both basic and instrumental activities of daily living (continuous variables) relates to medical, physical/functional, psychological, social and cognitive aspects of frailty. Modification over time in these measurements also consist major clinical outcomes.

2.5 Physical condition domain

The items that are evaluated in the physical condition domain are:
- the evaluation of the balance (dichotomous variable), reflecting physical/functional and possibly medical aspects of frailty. Similarly goes for lower limb strength (continuous variable).
- The performance to the Timed get Up and Go (TUG) test (continuous variables), revealing physical/functional frailty, but also related to cognitive aspects (30–32).
- the gait speed (continuous variable) is considered by many researchers even as a single item for the evaluation of frailty and the prediction of unfavorable major outcomes (31,33–39). Typically expressing physical/functional level of frailty, it is

considered as a more general index of a person's medical condition, often reported also as the sixth vital sign (40,41). With its dichotomous variation in normal and abnormal values, it constitutes another of the Fried's criteria of frailty.
- the grip strength (continuous variable with possibility also to dichotomization according to given normal values), reflects mostly physical/functional and secondarily medical aspects of frailty. It consists another of the Fried's operational definition's criterion of frailty (1,22,42).
- the low physical activity (dichotomous variable), as evaluated in another Fried's criterion, reflecting physical/functional, medical and possibly social and psychological aspects of frailty (1).
- the number of falls in the last year (continuous variable) expresses physical/functional frailty as an important clinical outcome, can be related to several medical conditions including iatrogenic side-effects and has also psychological implications in the form of the post-fall syndrome (43–46).
- the number of fractures in the last year and in adult lifetime (continuous variable) expresses physical/functional and medical frailty(47,48). Its evaluation in two time periods provides a dynamic index, revealing possible physical status degradation.

2.6 Nutritional domain

The items that are evaluated in the nutritional domain are:
- BMI (Body Mass Index) too low (dichotomous variable): values of BMI under 21, and especially under 18 are considered an index of malnutrition (49,50), reflecting medical, psychological, physical/functional and probably cognitive and social aspects of frailty.
- BMI too high (dichotomous variable): values of BMI over 30 are considered like obesity indication, even though sarcopenic obesity (51–54) cannot be excluded. Similarly to low BMI, this item reflects medical, psychological and probably cognitive and social aspects of frailty, with the physical/functional aspect having a dominant implication, since obesity leads to mobility problems.
- the high waist circumference (dichotomous variable), more than 88cm for women and more than 102 for men, representing a component of the metabolic syndrome (54), reflects medical frailty, but also, under the prism of obesity, enters the psychological, physical, cognitive and social aspect.
- the lean body mass (continuous variable) expresses the risk of sarcopenia, leading feature of frailty (55–57), and reflects medical, physical/functional and probably psychological aspects of frailty.
- the MNA score is initially obtained as a first step screening tool. That being ≥12, is indicative of normal nutrition (dichotomous variable) and no further testing is required. In case of MNA screening <12, the total MNA score is calculated (continuous variable) and if <17 (dichotomous variable) is indicative of bad nutritional status (58,59). Undernutrition is an index of medical, psychological, as well as physical/functional, cognitive and social frailty (60,28,61–63).

2.7 Cognitive domain

The items that are evaluated in the cognitive domain are:
-the MMSE (Mini Mental State Examination) (continuous variable) reflects mainly cognitive frailty, but can also be affected by the educational level psychological or medical problems (64).
-the MoCA (Montreal Cognitive Assessment) as a continuous variable mainly reflects cognitive frailty and can provide evidence of mild cognitive impairment (MCI) if dichotomized at the cut-off point of ≥26: normal and <26: cognitive impairment. The MoCa test is, similarly to MMSE, affected by educational level, psychological and medical problems. In general the MoCA can better detect cognitive frailty in persons at higher educational level (65,66)
-the subjective memory complaint (dichotomous variable) is often considered a prodromal sign of cognitive decline (67,68) , but can also be related to psychological, medical and social frailty.
- the natural language analysis can provide evidence for cognitive and psychological frailty.

2.8 Psychological domain

The items that are evaluated in the psychological domain are:
- the GDS-15 (Geriatric Depression Scale- 15 items) (continuous variable), mainly reflects the psychological domain, but can be also associated with social and cognitive frailty.
- the self-rated anxiety (continuous variable), reflecting psychological, social and cognitive frailty.
- the natural language analysis can provide evidence for cognitive and psychological frailty.

2.9 Social domain

The items that are evaluated in the social domain are:
-the living conditions (categorical variable) reflecting the social, psychological, physical/functional and medical domains of frailty.
-the number of leisure activities (continuous variable) and the membership in a leisure club (dichotomous variable), reflecting the social, psychological, physical/functional and partially the medical domains of frailty.
-the number of visits and social interactions (continuous variables) per week, reflecting social, psychological, physical/functional and medical aspects of frailty.
-the number of telephone calls exchanged and time spent on phone and on video-communication means (continuous variables) per week, touching the domains of social, psychological and medical frailty in case of sensory organ problems.

-the number of written messages sent by the participant (continuous variable) per week, reflecting mainly social, psychological but also medical and physical/functional aspects of frailty in case of sensory organ or dexterity problems.

2.10 Environmental domain

The items that are evaluated in the environmental domain are:
- the subjective suitability of the housing environment by the participant and the investigator (categorical variables), touching social, physical/functional and medical aspects of frailty.
- the number of steps to access the house (continuous variable), expressing accessibility issues and reflecting physical/functional, social and medical aspects of frailty.

2.11 Wellness domain

The items that are evaluated in the wellness domain are:
- the self-rated quality of life (continuous variable), reflecting aspects of psychological, social, medical, physical/functional and cognitive frailty.
- the self-rated health status and the self-assessed change in health status in the last year (ordinal variable), reflecting aspects of medical and psychological frailty.
- the self-rated anxiety level (continuous variable), reflecting psychological, social, medical, physical/functional and cognitive aspects of frailty.
- the self-rated pain scale (continuous variable), reflecting medical, physical/functional and psychological aspects of frailty.

3. Technical metrics

The FrailSafe system devices are used during the lending of the material to the participants houses (FrailSafe sessions) and provide the technical metrics that are integrated into the FrailSafe system database.
Several technical devices and applications provide metrics that are translated into meaningful clinical measurements and, likewise the clinical metrics, reflect variable domains of frailty.
Table 2 presents the items recorded by the FrailSafe system devices and their clinical translation and inter-relationship tags with the aspects of frailty.

Table 2. Technical metrics. Variables monitored, their clinical relevance and frailty aspects' tagging.

FrailSafe device/ application	**Variables monitored**	**Clinical relevance with frailty aspects' tagging**
Sensorized strap/vest	ECG measurements:	Heart rate variability in response to the activities (M, P, ψ)
	IMU measurements:	Detection of falls and of fall risk (P, M) Activity classification (P, M, s)
	Respiration movements:	Breathing amplitude and respiratory rate variability in response to the activities (M, P, ψ)
	Activity attributes:	Activity monitoring, activity patterns' recognition (P, M, s) Distances covered (P, M, s) Gait speed (P, M, c)
GPS logger	Speed of movement Distance covered while being outdoors Distance away from starting point	Gait speed (P, M, c) Indication for vehicle usage (P, c) Activity pattern (P, M, s)
Beacons	Aggregated time passed in each room	Each room usage, indication of time repartition during the day between activities that are mostly attributed to certain rooms of the house. Indirect index of indoors activity (S, P, ψ)
Red-wings serious game	Average grip strength Maximum grip strength Time applying optimal grip strength Total distance covered Total time played	Grip strength, indicating overall body strength (P, m) Stamina (P, m) Cognitive function (executive function, reflexes, information and reaction treatment speed and efficacy, concentration) (C) Brain-motor coordination and efficacy (C, P)
Virtual supermarket serious game	Total time played and wondering into the virtual supermarket Errors in the types and quantities of the items bought Errors in the paying process	Executive function, visual and verbal memory, attention, spatial navigation (C)
Blood pressure monitoring	Blood pressure Heart rate	Cardiovascular parameters (M)
		Continuous in the next page

Tags (reflecting impact of each item on each of the aspects of frailty)
Physical/functional: P dominant, p recessive
Medical: M dominant, m recessive
Social: S dominant, s recessive
Cognitive: C dominant, c recessive
Psychological: Ψ dominant, ψ recessive

3.1 Sensorized strap/vest (WWS and WWBS)

The sensorized strap/vest which is manufactured by Smartex is equipped with a series of sensors which provide useful measurements for FrailSafe participants. These measurements can be grouped in these categories:

3.1.1 ECG measurements:

The main measurement of this category is the value of the ECG signal coupled together with a quality index which shows how accurate the measurement actual is. This helps ignoring measurements for which the quality is low because strap was not placed properly. Using the ECG signal, the vest software calculates useful clinical measurements such as Heart Rate, Heart Rate Variability, and R-R interval distance in ECG signal. These metrics, expressing cardiovascular activation patterns, in clinical terms, reflect mainly on medical, physical/functional and maybe psychological aspects of frailty.

3.1.2 IMU measurements:

The strap is equipped with a “light” IMU measuring only the participant’s specific force in X-Y-Z axis (using an accelerometer), while he/she is wearing the strap. The new vest is equipped with 3 IMUs, each one of which is capable of measuring the participant’s specific force, angular rate, and the magnetic field surrounding the body in X-Y-Z axis using accelerometer, gyroscope and magnetometer, respectively. These measurements are might not be directly connected with clinical parameters, however they are needed in order to run Fall Detection and Activity Classification algorithms. These metrics, expressing activity patterns, in clinical terms, reflect mainly on medical, physical/functional and probably social aspects of frailty.

3.1.3 Respiration measurements:

The strap is also equipped with a piezoelectric point placed on the thorax, which is used to measure the pressure on the thorax caused by the participant’s breathing. The strap uses this measurement to calculate the Respiratory Rate, and the Breathing Amplitude of the participant. These metrics, expressing cardiorespiratory activation patterns, in clinical terms, reflect mainly on medical, physical/functional and maybe psychological aspects of frailty.

3.1.4 Activity attributes:

Additionally some measurements are provided about the activity the participant performs while wearing the strap. There is a simple activity recognition (lying, standing, walking, running) which however is not as accurate as the activity classification algorithm developed by the UoP. Also there is a counter measuring the number of steps the participant has done while wearing the strap, and the step period which shows how fast/slow the steps are being done. These metrics, expressing activity patterns, in clinical terms, reflect mainly on medical, physical/functional and probably social aspects of frailty. For gait speed detection, a cognitive component could be implied.

These measurements are summarized in the table 3.

Table 3. Measurements performed by the sensorized strap/vest.

<table>
<tr><th>Measured parameter</th><th>Type</th><th>Extracted clinical measurements (examples)</th><th>Analysis using data mining techniques</th></tr>
<tr><td>Electric signal measuring the ECG
ECG signal quality
➢ Heart rate
➢ R-R intervals
➢ Heart rate variability</td><td>ECG measurements</td><td>Average heart rate / day, maximum heart rate / day etc.
(this can be connected with the activity class and generate measurements such as average heart rate / day while walking etc)</td><td></td></tr>
<tr><td>Accelerometer in X-Y-Z axes</td><td rowspan="3">IMU</td><td rowspan="3">Patterns of (slow/fast) movements such as walking, falls etc</td><td rowspan="3">Activity classification (standing/sitting, lying, walking, walking upstairs, walking downstairs)

Fall detection</td></tr>
<tr><td>Gyroscope in X-Y-Z axes</td></tr>
<tr><td>Magnetometer in X-Y-Z axes</td></tr>
<tr><td>Electric signal measuring the chest pressure on the piezoelectric point
Respiration signal quality
➢ Breathing rate
➢ Breathing Amplitude</td><td>Respiration measurements</td><td>Average breathing rate / day, maximum breathing rate / day etc.
(this can be connected with the activity class and generate measurements such as average breathing rate / day while walking etc).</td><td></td></tr>
</table>

Activity performed Estimation of energy activity Step period Pace (number of steps)	Activity attributes (calculated by Smartex using IMUs)	Steps, step period	

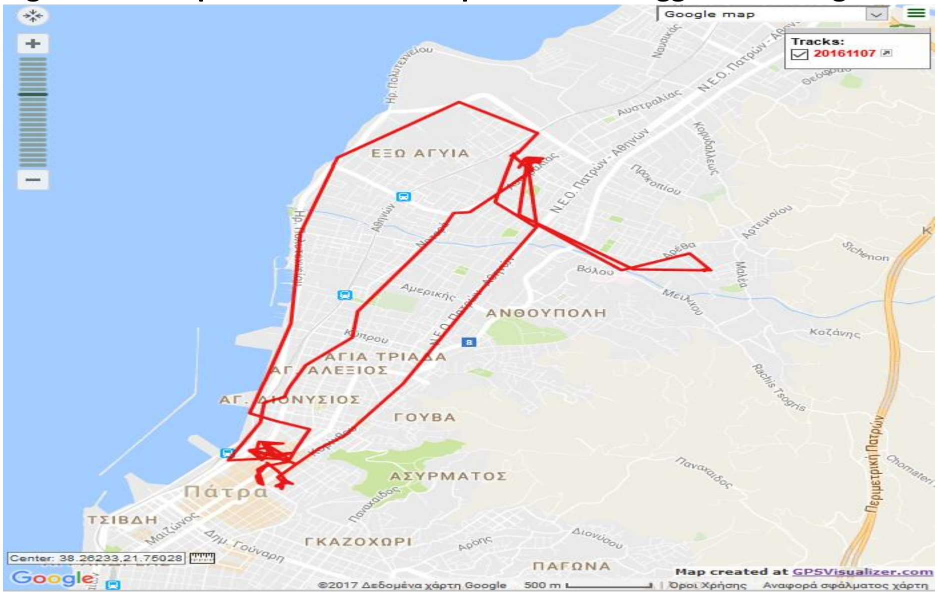
3.2 GPS logger (smartphone)

The GPS (Global Positioning System) logger application for the smartphone collects the measurements about the geographic location of the participants. The location is obtained by receiving a signal from GPS satellites, thus it is accurate only for the outdoor localization of the participant (in a macroscopic scale). The specific measurements obtained are the latitude, longitude, and elevation of each geographic location, together with the accuracy of the measurement and the orientation of the movement. The GPS logger application additionally measures the number of steps the participant has made, using the phone sensors. Combining subsequent points of the location of the participant, we can derive to other measurements with more clinical value such as the speed of movement and the gait speeds, the distances covered, the usage of vehicles and the maximum distances from the starting point expressing a large amplitude of locomotion patterns. These measurements can indicate physical/functional, medical, social and even cognitive aspects of frailty.
The measurements performed by the GPS logger are summarized in the table 4.

Table 4. Measurements performed by the GPS logger.

Measured parameter	**Extracted clinical measurements (examples)**	**Analysis using data mining techniques**
Latitude Longitude Elevation Speed Accuracy Bearing (orientation) Steps	Speed of movement, distance covered while being outdoors. Based on the speed, there is an indication if the participant is walking, on a vehicle etc.	Attempt to correlate the outdoor moving patterns of the participants with the frailty status

Figure 2. Example of the visual output of a GPS logger recording.



3.3 Beacons

One of the partners (CERTH) has developed an application for the smartphone, which can be used with the beacons to perform indoors localization of the participant. Each measurement obtained from the developed application contains the room name that the participant is located. Combining subsequent measurements, we can derive the information of the aggregated time the participant has spent in each room. On clinical terms this could be an indication of the time repartition during the day between activities that are mostly attributed to certain rooms of the house. This indirect index of indoor activity could reflect social, physical/functional of psychological aspects of frailty.

3.4 Serious games

The flappy/red wings serious game has been developed by Brainstorm and records a log file with measurements connected with the game such as the speed that the flappy is moving, the distance it has covered, the height which is at, and the number of lives the player still has. Additionally, as the game is operated by the dynamometer, the force of the participant is being recorded. Combining the subsequent measurements of the log files, we can derive the total time the participant played the game, the total distance covered (total score), and the maximum grip strength on the dynamometer.

In clinical terms, these measurements express the grip strength and stamina, indicating overall body strength, reflecting medical and physical/functional aspects of frailty but also some elements of the cognitive function, like the executive function, the reflexes, the information and reaction treatment speed and efficacy

and the concentration. This serious game, is actually an exergame, that could also give indices about the brain-motor coordination and its efficacy, reflecting both the physical/functional and the cognitive aspect of frailty, although sometimes restricted by biasing medical local conditions (wrist arthritis).
The measurements derived by the red wings serious game are summarized in table 5.

Table 5. Measurements performed by playing the flappy/red wings game.

Measured parameter	**Extracted clinical measurements (examples)**	**Analysis using data mining techniques**
Distance Height Lives Grip strength	Average grip strength, Maximum grip strength, time applying upper limit grip strength, total distance covered, total time played	**Personalized analysis**: If the participant wears the sensorized vest while playing the game, we could correlate the vest measurements (heart rate, respiration rate) with the grip strength applied **Population analysis**: Correlation of the overall performance score with cognitive and physical domain.

Another serious game proposed to the participants is the virtual supermarket (VSM) game, developed by CERTH (figure 3), which is played on the tablet and mimics the activity of going for everyday shopping. It provides aggregated measurements for the whole session, such as:
- total time played and wondering into the virtual supermarket
- number of items listed in the shopping list (types and quantities)
- number of items bought from the supermarket (types and quantities)
- value of items in shopping list
- money paid by the participant

By these metrics, we derive scores that correspond to the correct items purchased, the, the correct quantities, the erroneous buyings outside those unlisted, the duration of the shopping procedure, the correct payment and the errors committed in money exchange.

Figure 3. The virtual supermarket game. Example of the display of the game, at the stage of paying.

The VSM game is aimed at testing a multitude of cognitive processes namely visual and verbal memory, executive function, attention, and spatial navigation with the emphasis placed on executive function. The performance of users in the game has been shown to be related to indications of MCI (69). In this respect, it is a valuable tool to monitor the cognitive function of the users, and reflect cognitive aspects of frailty.

4. The integration of the components of the FrailSafe study

The technical metrics derived from the FrailSafe devices, come to be added on the top of the clinical evaluation metrics for each participant (Figure 4), both contributing to the construction of the VPM (Virtual Patient Model). The technical metrics are about to be evaluated for their supplementary contribution in the detection of frailty, tested for their performance as frailty indices and for their ability to be used as frailty biomarkers. Their advantages, like the large-scale objective date collected in real-time ecological monitoring conditions and their integrated multilevel analysis, bear significant promise (Figure 1). All measurements of the FrailSafe devices are well documented in terms of time they occur and by this means they can be easily correlated with simultaneous recording from the rest of the FrailSafe devices. Moreover, by a daily clinical phone follow up during the FrailSafe session, we could potentially relate clinical events and symptoms with technical devices' metrics, even though with a rougher and less precise way, offering possibilities for their interpretation in a short-term scale.

On the other hand, in a long-term and perhaps more meaningful context, clinically meaningful events and changes in the general health status, reflecting loss of reserves, represent measurable outcomes of the study (as described in the revised version of D2.1 Clinical Study Methodology) and eventually consist the endpoints of interest that serve as “gold standards” for the validation of the technical metrics. Throughout the course of the clinical follow up of a person, new metrics are accumulated and enter the integration system (Figure 4). The repetitive monitoring with the FrailSafe devices aims at detecting even minor and discreet changes and identifying the optimal frequency for the cost-effectiveness of the application of the FrailSafe system. Possible changes detected by the FrailSafe devices (technical index delta) aspire to be more precise, earlier and more pertinent and will be tested for their relevance in predicting the clinical evolution (clinical index delta).

The output result of the integration of all available metrics into the FrailSafe system is tested for its ability to measure and predict high-risk profiles and also to determinate their special characteristics. This could contribute to the early recognition of worrisome evidence in the course of a person’s follow up and thus precisely aim at repairing reversible situations. By this means, frailty prevention strategies could be targeted and applied early in the disease course, for the prolongation of autonomous and dependence free living.

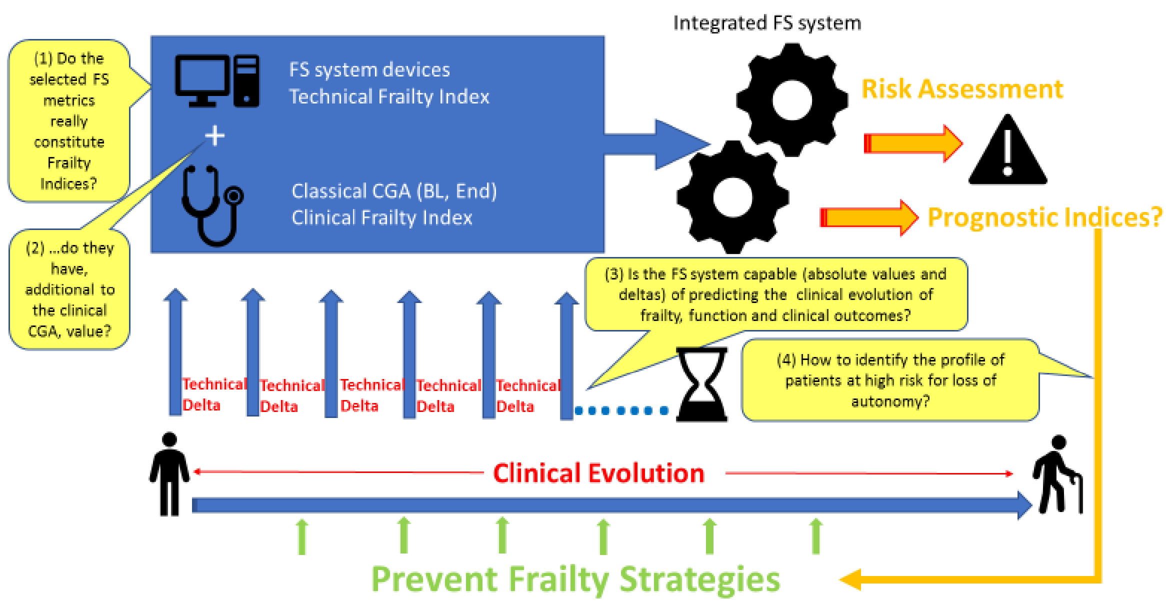


Figure 4. Clinical study’s rough architecture and main clinical objectives. Individuals are followed up over a certain amount of time, during which several clinical and technical measurement are obtained and fed into the integrated FrailSafe system. Main study issues are (1) if the selected new technical metrics could serve as frailty indices, (2) if they have added value on the top of the conventional CGA, (3) if their timeshots and deltas in the course of time are capable of predicting clinical outcomes and frailty transition stages and (4) if they could be used to early identify high-risk profiles for autonomy loss in order to contribute to the planification of frailty prevention strategies. *FS: FrailSafe*

5. The integration process in terms of data analysis

The integration of FrailSafe's multimodal data is based on the development of a management infrastructure with modular services and patient-specific applications, as well as the development of novel methods for offline fusion and analysis of advanced technology data. The large data files that contain the raw sensor data generated by the devices, the medical records, and the analysis results produced by medical experts or by developed software, are stored effectively, fulfilling the data access requirements that arise during offline analysis. The data are then aggregated as shown in Figure 5, and are used to create a Virtual Patient Model, which will guide the clinicians to the design of their interventions.

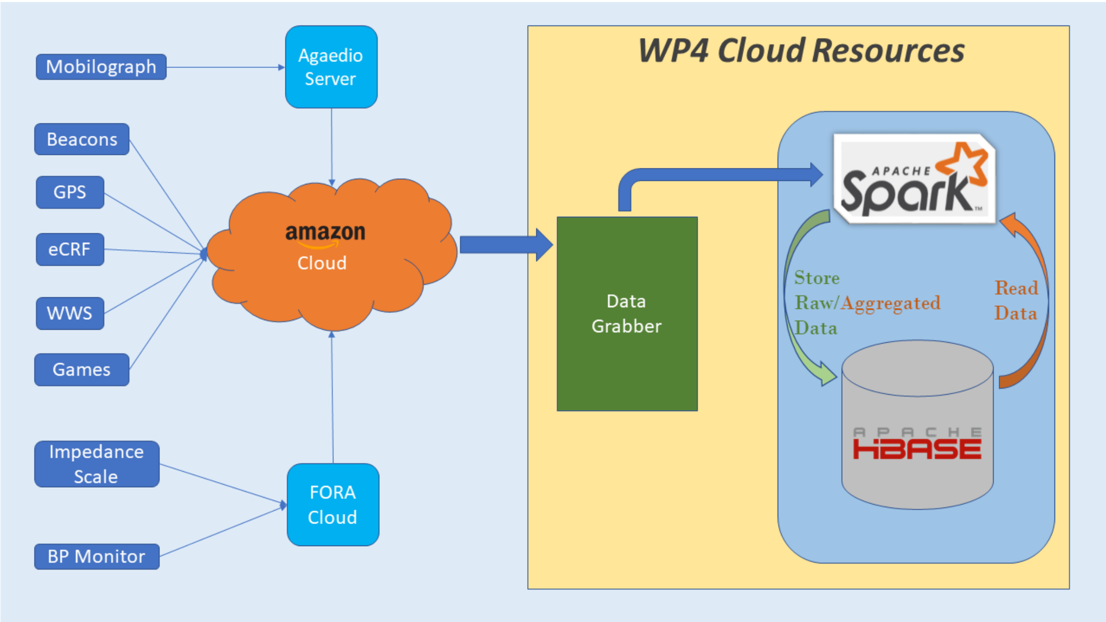


Figure 5. WP4 cloud resources for data collection and aggregation.

In the heart of the aggregation and storing system is a cluster of 4 Amazon EC2 machines, which runs Apache HBase as a distributed NoSQL database and uses Apache Spark for data processing and aggregation. There is an additional Amazon EC2 machine called the "Data Grabber", which is responsible to collect the data uploaded to the Amazon cloud by the different submodules of the FrailSafe project, or the external servers of the machine vendors (Agaedio and FORA).

Apache HBase was selected because it is part of the Hadoop ecosystem, which provides high scalability in data analysis and knowledge discovery algorithms. Specifically, Hadoop is an open-source software framework used for distributed storage and processing of big data using the MapReduce programming model. It consists of computer clusters built from commodity hardware. All the modules in Hadoop are designed with a fundamental assumption that hardware failures are common occurrences and should be automatically handled by the framework.

In respect to the subsequent (offline) data analysis, we followed two pathways, (i) analysis of clinical data from the eCRF platform and (ii) analysis of multi-scale and multi-dimensional recordings from the sensors. The clinical data from the eCRF platform were firstly used to identify global group differences in the population. To that end, a group-wise univariate analysis was performed across three different splitting factors: a. Frailty status-based analysis, b. Age-based analysis and c. Gender-based analysis. Secondly, the clinical measurements from eCRF were used for multivariate statistical analysis. Specifically, their predictive ability towards the development of a frailty index was examined. Two different frailty indexes (FI) were computed, one aiming to predict the discrete Fried classification score (FI1) and one trying to estimate a continuous score as a linear combination of the 5 criteria (involuntary weight loss, slow walking speed, poor handgrip quality, reported exhaustion, low physical activity) related to Fried classification (FI2). The ultimate goal is to investigate whether the proposed frailty indexes are more reliable predictors of frailty transition than standard classification scores. The prediction models were built using Lasso regression after performing data imputation to fill in missing values and variable standardization. Spearman's rank correlation coefficient between Fried's score and the proposed FI1 score was 0.73, whereas Spearman's correlation between the 5 criteria related to Fried classification and the calculated FI2 score was 0.66.

Finally, multi-dimensional time series analysis has been targeted for classification of activities of daily living (ADL) aiming at prediction of frailty in our subsequent work. For the former, a human motion identification module was developed which classifies basic ADLs (walking, walking-upstairs, walking-downstairs, sitting, standing and laying). The multiclass prediction model uses a high-dimensional signature extracted in time and frequency domain from each frame, to classify it during testing. Classification was based on a two-step procedure in which the individual decisions were weighted by their sensitivity on the training set and finally combined by a fusion function. For prediction of a frailty, some preliminary work has started on the investigation of deep learning techniques for seamless extraction of a features' hierarchy towards an in-depth analysis of the time series data.

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