FRAilty incidence in surGIcal European patients (FRAGILE) European prospective cohort study of the prevalence of frailty in surgical patients.

VERSION 5.0 December 2020

Principal Investigators: César Aldecoa Álvarez-Santullano; Carlos Ferrando Ortolá

Title of the project: FRAilty prevalence in surGIcal European patients
European prospective cohort study of the prevalence of frailty in surgical patients.

This study is endorsed by the Spanish Multimodal Rehabilitation Group (GERM), REDGERM, and the Spanish Society of Anesthesiology (SEDAR)

REDGERM

SOCIEDAD ESPAÑOLA DE ANESTESIOLOGÍA, REANIMACIÓN Y TERAPÉUTICA DEL DOLOR

1. SUMMARY

Short title: FRAGILE

Methods: European prospective one day cohort study. Analysis of the prevalence of frailty and predefined 30-day postoperative complications in adult patients undergoing emergency or elective surgery.

Investigation sites: European hospitals where elective or emergency surgery is performed, where preoperative frailty index can be determined and patients can be followed for 30 days.

Objectives 1) To collect data on the incidence of patient frailty in elective and emergency surgery. 2) To evaluate the association between frailty and postoperative complications, hospital stay, quality of life (QoL) and mortality. 3)To evaluate whether the implementation of perioperative prehabilitation and early rehabilitation programs (posthabilitation) affects postoperative complications, QoL and frailty state at 30 days.

Number of patients: We aim to collect a sample size of 6500 in order to adequately represent the frailty prevalence (for a expected proportion de 0.1, with this sample, the total width of 95% confidence interval would be 0.015). For the second part of the study, this sample size was assessed in relation to the outcome with the lowest frequency, ie. thirty-day mortality. Assuming a global incidence of frail patients of 10% in our population with an expected 30-day mortality of 4% in the non-frail group, a sample size of 5000 patients allows us to significantly detect, two side 95% confidence interval and 80% power, a relative risk (RR) of 1.8 (7% of expected thirty-day mortality in frailty population).

Inclusion criteria: Patients over the age of 18 who will undergo emergency or elective surgery with an intended hospital stay of more than 24 hours and any type of anesthesia.

Statistical analysis: Continuous variables will be described by a mean and standard deviation if they present a normal distribution; by a median and interquartile range if they are not normally distributed. The comparison of continuous variables will be performed using one-way ANOVA or the Mann-Whitney test, as needed. Univariate analysis will be used to test factors associated with postoperative complications, hospital stay and in-hospital mortality. Univariate analysis and multivariate logistic regression models will be built in order to identify factors independently associated with these results and in order to adjust differences among confounding factors. Factors will be introduced into the model based on their relationship with the univariate result ($p < 0,05$), biological plausibility and low rate of missing data.

2. RESEARCH TEAM

2.1 CENTRAL COORDINATION

Central Coordinators REDGerm Principal Investigators:	**Cesar Aldecoa Alvarez-Santullano** Hospital Universitario Rio Hortega, Valladolid 657500031 Email: cesar.aldecoa@gmail.com **Carlos Ferrando Ortolá** Hospital Clínic de Barcelona 609892732 Email: caferoanestesia@gmail.com
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3. BACKGROUND AND JUSTIFICATION

Frailty is defined by the deterioration of physiological functions of multiple systems in the body. This leads to an increased vulnerability for adverse events, increased dependence and medical complications including death, especially when the body is subjected to stress (1,2). Although numerous studies have described the prevalence of frailty and its association with age, specifically those over the age of 65 (3, 4, 5), there is an association between frailty and the incidence of complications in young patients, with an increase in the prevalence of comorbidities in patients under 40 years of age (6,7).

Therefore, frailty has been identified as an important risk factor that affects clinical outcomes in younger surgical patients (7). Several studies have suggested that high preoperative frailty scores are independently related to an increase in postoperative complications, length of hospital stay, 30 and 90-day mortality and the likelihood of institutionalization (8,9).

In a recent retrospective study including 232.352 patients above the age of 65, Mosquera et al (5) found that frailty increased mortality up to 6 times with respect to non- frail patients. This finding is consistent with other investigations in different surgical procedures (10). The association between frailty and surgical complications is consistent, frail patients have a risk of surgical complications up to twice as high as non-frail patients (5,9,11-13). Furthermore, an increase in hospital stay of up to 4 times of frail compared to non-frail patients has been found (5, 12).

For all these reasons, measuring preoperative frailty has a potential value in evaluating surgical risk and in applying pre and postoperative measures aimed at improving patient outcomes.

The standardization of perioperative care bundles, like intensified recovery bundles in surgical patients, has been associated with a decrease in complications and process costs (14-15). However, with regards to frailty, studies proving specific measures that reduce frailty indices and improve clinical outcomes are lacking.

Although the prevalence of frailty in patients older than 65 is estimated at about 20% (16), no prospective data evaluating the prevalence of frailty in the wider surgical population exists. In a recent retrospective study, Mrdutt M et al (17) observed a prevalence of frailty of 5.6% and an association with a significant increase in surgical complications, hospital stay, mortality and costs. The prevalence of pre-frailty states of frailty in this cohort was almost 47% which are also associated with poorer outcomes.

Our goal is to carry out a one day international point-prevalence

multicenter cohort study in patients over the age of 18 who will undergo emergency or elective surgery in order to acquire detailed data that describes the prevalence of frailty and its association with postoperative complications, mortality, hospital stay and quality of life at 30 days. Furthermore, we will determine if the application or not of routine measures during the perioperative period affects postoperative complications and quality of life at 30 days.

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5. OBJECTIVES

Primary objective

To evaluate the incidence and degree of frailty in a population of patients undergoing programmed or emergency surgical interventions that require hospital admission.

Secondary objectives

1. To evaluate global frailty prevalence by age groups.
2. To evaluate the association between the presence and degree of frailty, and postoperative complications, hospital stay and 30-day mortality.
3. To describe the relationship between the degree of frailty and quality of life 30 days after surgery.
4. To describe the association between frailty and postoperative cognitive disorder and delirium by age groups.
5. To evaluate if the routine implementation of a preoperative prehabilitation program in the subgroup of patients programmed for surgery and its relationship with frailty and postoperative outcomes.
6. To evaluate the routine implementation of early rehabilitation measures in surgical patients and its relationship with frailty and postoperative outcomes.
7. To describe the relationship between each predefined item of prehabilitation and postoperative rehabilitation with clinical outcomes, including complications, hospital stay and quality of life at 30 days.

6. METHODOLOGY

TYPE OF STUDY

European observational prospective 1 day cohort study, with a 30 day follow-up of patients who meet criteria in participating hospitals. Each national group will select a single 1-day patient recruitment period during predefined months in 2020.

Adittionally, due to pandemic SARS-COV-2 and the associated reduction of sheduled surgery Activity, it could be necessary to add a second day of recruitment in order to achieve the adequate simple size of the study.

Inclusion criteria

All consecutive patients over the age of 18 who will undergo emergency or elective surgery under general anesthesia and/or locoregional anesthesia (central neuroaxial blocks or locoregional anesthesia) with an expected hospital stay of at least 24h.

Exclusion criteria

Outpatient (ie. day case) surgery, obstetric analgesia or anesthesia, organ transplant surgery, cardiac surgery, neurosurgery.

7. STUDY PROCEDURES

Consent procedures

Written informed consent will be obtained from all subjects who voluntarily participate in the study. Consent procedures and provision of patient information will be conducted in accordance with local practice. Nevertheless, in some countries it may be possible to successfully seek a waiver of individual patient consent from an appropriate regulatory authority.

Specific regional procedures for the recruitment of patients and the request of consent. When necessary, the FRAGILE protocol will include appendices specific to each autonomous community or country describing specific procedures related to the utilization of data, the identification of patients, the procedures involved and the necessary regulatory approvals.

Study data

Data will be collected in all patients included in FRAGILE. All necessary data is included in an annex.

For the realization of sub-studies related to FRAGILE, each group or hospital may complete the basic data with a limited number of additional variables if they can be included in the case report form (CRF) as long as they meet the study regulations, and with the approval of the principal investigators and the FRAGILE Audit Directive Committee. All FRAGILE investigators will be informed of the selection process of related sub-studies ad hoc.

Data collection

Data will be collected in each hospital on an individual paper CRF for each patient recruited. Paper CRFs will be store in a locked office in each center. The local principal investigator or national coordinator will responsible of these CRFs will be. This will include patient identification data in order to allow follow-up of clinical results. Study data will be pseudonymized by encryption, generating a unique numerical code prior to entry to an online database via an electronic CRF (eCRF). The Castor EDC platform will be used to collect the data https://www.castoredc.com/. Castor EDC complies with all applicable laws and regulations: good clinical practice (GCP), 21 CFR Part 11, annexed 11 of the European Union and UE and the European Directive on data protection.

Each patient will only be identified in the eCRF by their numerical code. Therefore, the research coordination team will not be able to associate data to an individual patient without contacting the local team. In each center there will be a list of individual patients and their identification codes in the database in order to track clinical results and provide any data that might be missing. Once the local coordinator has confirmed the data entry is complete for their hospital, they will receive a spreadsheet with unprocessed data, this will allow more data integrity and precision controls. Individual data at each hospital may be used by local investigators, however, they may not be published on an individual basis under any circumstance.

All identifiable data collected, processed and stored for the purposes of the project will be kept confidential at all times and will comply with the guidelines of Good Clinical Practice for Research (GCP) and the General Regulation of Data Protection (GDPR) (Regulation (EU)) 2016/679).

Study organization

FRAGILE will be directed by the study management group, that will be responsible for the administration of the study, the communication among project partners, monitoring and data management.

The coordinators of each European country will manage and lead the project in their respective countries and will play the following roles:

- Identifying local coordinators in participating hospitals.
- Ensuring the distribution of documentation, bibliography and other study material.
- Ensuring that necessary regulatory approval is obtained before the start date.
- Ensuring good communication among the participating sites in their community. (In large communities more than one coordinator may be appointed).

Local coordinators in individual institutions will have the following responsibilities:

- Providing leadership for the study in their institution.
- Ensuring that necessary regulatory approval is obtained for their particular institution.
- Guaranteeing adequate training of all participating personnel before data collection.
- Supervising daily data collection and helping in problem solving.
- Acting as a guarantor of the integrity and quality of the data collected.
- Ensuring the appropriate termination of CRFs by supervising the data entry on a local level.
- Communicating with the coordinator of the correspondent national coordinator.

Definition of study completion

The completion of the study is defined at 30 days of follow-up for the last patient included in FRAGILE. The data analysis will be adjusted accordingly.

STATISTICAL ANALYSIS

Sample size calculation

Our plan is to recruit as many European centres as possible and ask them to include in the study all elegible patients with inclusion criteria. Only those centres that include at least 10 valid patients will be included in the analysis.

The sample size was calculated to detect the effects of frailty over the outcome with the lowest prevalence: thirty-day mortality (4% prevalence in no-frail patients). Estimating a global incidence of frail patients at 10% in our population, a simple size of 5000 patients allows us to significantly detect with a relative risk (RR) of 1.8, 80% power, two side 95% confidence interval and 97% accuracy. Taking into account a possible loss of patients of 30% during the follow-up period, the final simple size will be adjusted to 6500 patients

Statistical analysis

Data will be presented at European level. All data will be anonymized prior to publication.

Categorical variables will be presented as proportions and will be compared using chi-square or Fisher exact tests. Continuous variables will be presented as mean and standard deviation or as median and interquartile range, depending on the distribution of the variables. Continuous variables will be compared using one-way ANOVA or Mann-Whitney U test. A univariate analysis will be performed in order to test variables associated with postoperative complications, hospital length of stay and in-hospital mortality. Univariate analysis and hierarchical multivariate logistic regression models will be built in order to identify which variables are independently associated with these results and to adjust for confounding variables. Variables will be introduced into the models based on their relation to the univariate analysis ($p<0,05$), biological plausibility and the low rate of missing data. A step by step approach will be adopted to introduce new terms. Logistic regression results will be presented as adjusted odds ratio (OR) with 95% confidence intervals. The models will be evaluated through sensitivity analyses in order to explore possible interacting variables and to examine any effect on the results. Only one final analysis is planned at the end of the study.

Data will be analyzed using the percentage of frail patients and both the

principal and secondary outcome variables. It will be evaluated the influence of the recorded variables. Initially, a univariate analysis will be performed in order to evaluate the relation between each factor and the outcome variables. Comparisons will be performed using chi-square tests for the categorical variables, whereas T tests and Kruskall-Wallis tests will be used to compare differences between normally and non-normally distributed continuous variables respectively. Hospital length of stay will be analyzed through the normal distribution logarithmic transformation and independent T tests with exponentiation, given its non-normal distribution. The multivariate analysis, using binary logistic regression for the postoperative complications and using linear regression with logarithmic transformation for the length of hospital stay, will be performed afterwards, to all variables that had a statistically significant difference or almost significant (P<0,1). P<0,05 will be considered as statistically significant.

Outcomes

Outcome definitions are described in the annex 2.

Primary outcome

The percentage of patients with frailty identified in the preoperative assessment in both elective and emergency surgery, as well as frailty's severity.

Secondary outcomes

- The incidence and severity of frailty stratified by age groups and type of surgery (elective and emergency surgery).
- The presence of in-hospital postoperative complications.
- All-cause in-hospital mortality (censored at 30 days after surgery).
- The compliance with preoperative and postoperative prehabilitation programs.
- Length of hospital stay (length of hospital stay after the primary surgery).
- Quality of life 30 days after surgery.
- Presence and severity of frailty 30 days after surgery.

Blinding

Because of the study characteristics assessors will not be blinded. Data will be obtained extracting it from the clinical records and asking patients through a personal interview or by phone call.

Planning:

	Pre-operative	Day of Surgery	30 postoperative day
Demographic and baseline data	x		
Morbidity scales*	x		x
Intraoperative data		x	
Postoperative outcomes			x

*Includes clinical frailty scale, frail questionary, Barthel scale, Charlson index, cognitive evaluation and EuroQOL. In the supplement is specified which ones are done preoperatively and/or postoperatively.

ETHICS

This trial has been designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council relating to human rights and biomedicine, and the Universal Declaration of UNESCO on the human genome and human rights, and with the requirements established by Spanish legislation in the field of biomedical research, the protection of personal data, and bioethics.

National coordinators and principal investigators at each participating centre will be responsible for clarifying the need for approval by the local Ethics Committee.

Data registration without confirmation of ethical or other regulatory approvals will not be permitted. The Steering Committee will provide the informed consent form approved by the regulatory CREC (Clinical Research Ethics Committee) and it encourages all investigators to inform patients about their participation in the study, although in some countries it may be possible to successfully seek a waiver of individual patient consent from an appropriate regulatory authority.

SAFETY CONSIDERATIONS

There are no safety considerations related to the FRAGILE study. There is no risk of harm neither to patients nor to investigators.

SAFETY

The study presents no risk to patients and investigators. Adverse events are not monitored and they do not need to be reported in a different way than that of the

usual clinical practice.

MONITORING AND AUDIT

The FRAGILE study master files will be audited by the sponsor (Grupo Español de Rehabilitación Multimodal) to ensure that the study's activities are performed in accordance with the protocol, the sponsor's standard operating procedures, Good Clinical Practices and the applicable regulatory requirements. In the participating hospitals, local study documents can be selected to perform a local audit. Nevertheless, the FRAGILE study team will not routinely supervise the participating hospital's individual data collection or data verification.

8. STUDY COMMITTEES

Study management group

The FRAGILE study will be managed by RedGERM, belonging to Grupo Germ,

Steering Committee

The study's Steering Committee shall appoint an independent president on behalf of the GERM's Scientific Committee (Alfredo Abad Gurumeta) and the independent members (Jesús Villar). There is no role for a Data Monitoring Committee.

The Scientific Committee will be composed of the study's principal investigators.

RedGERM central coordinators and principal investigators:	**Cesar Aldecoa Álvarez-Santullano** Hospital Universitario Rio Hortega, Valladolid 657500031 Email address: cesar.aldecoa@gmail.com **Carlos Ferrando Ortolá** Hospital Clínic Barcelona 609892732 Email address: caferoanestesia@gmail.com
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9. FUNDING

The FRAGILE study lacks external funding.

10. COMPENSATION

The FRAGILE study will be promoted by the Grupo Español de Rehabilitación Multimodal (GERM), which has an insurance. Even though given the study's characteristics, an insurance is not considered necessary.

11. DISSEMINATION OF THE RESULTS

The Steering Committee will appoint a Drafting Committee to edit the scientific report(s), which will be disseminated in due course. The performance of secondary analysis is foreseen. FRAGILE investigators will have priority over the conduction of these analysis and they will be encouraged to do so. Participation will be based on the contribution to the primary study. The Steering Committee will consider the scientific validity and the possible impact on the participating centres' anonymity before granting any request. If necessary, prior written agreement will establish the terms of this type of collaboration. The Steering Committee shall approve the final version of all manuscripts before their presentation. In the event of disagreement within the Steering Committee, the head of the research project will make a choice. Any data of the analysis of

FRAGILE that includes two or more venues will be considered to perform possible secondary analyses and will be subject to predefined rules.
All study participants will be included as co-authors under the FRAGILE Network Group.

Data management and data property

The sponsor of the study, the **Grupo Español de Rehabilitación Multimodal**, will act as the custodian of data. In line with data preservation and data exchange principles, after the publication of the general database, the Steering Committee will consider all reasonable requests to conduct secondary analyses. Its decision will be based on the quality and validity of the proposed analysis. Only summary data will be publicly presented and all European, national, institutional and patient data will be absolutely anonymous. Individual patient data provided by the participant hospitals are the property of their respective institution. Once each local coordinator has confirmed that the provided data are both complete and exact, raw data will be transferred to spreadsheet. Complete datasets, concerning patients participants, hospitals and communities will be codified, nevertheless, they will be at public disposal during two years after the publication of the main scientific report. Before this, the Steering Committee is under no obligation to provide data for any participant investigator if the Committee considers that it is not in line with the overall objectives of the FRAGILE study.

12. STUDY TIMELINE

Data collection will start with the first recruited patient, once all required regulatory approvals are obtained.
The study will start the day of the surgery. Patients will be followed up for 30 days. The 30 days follow-up will be done through a patient phone call. The study will last 30 days from the inclusion of the patient. (Onset is yet to be determined).

13. EXPECTED RESULTS

The incidence of frailty within the overall surgical patients is not yet defined. The incidence of frailty according to age group also remains unclear. It has never been described whether or not there are differences between patients undergoing elective and urgent surgeries in terms of frailty. In general, the published reviews performed in patients older than 65 years old show that the prevalence of frailty in this age group is more than 20%; and it is associated with

an increase in postoperative complications, hospital length of stay and institutionalization. The relation between the application of prehabilitation protocols in frail patients and their postoperative evolution has been scarcely investigated and its association with postoperative quality of life remains unknown.

Likewise other large international cohort studies, the expected results of this study are:

1. To identify the incidence and severity of frailty in patients undergoing elective as well as urgent surgeries.
2. To identify whether the application of perioperative prehabilitation programs is associated with an improvement in the frailty state and in the clinical outcomes 30 days after surgery.
3. To identify postoperative complications in frail patients both at a national level and an international level.
4. To identify the differences in postoperative quality of life 30 days after surgery between frail and non-frail patients, and between the different degrees of frailty after urgent and elective surgery.
5. Overall, a high international participation is anticipated. Therefore, the obtained data will allow not only to clearly define the prevalence of frailty in different age groups, in different types of surgery and in urgent or elective surgery, but also to identify which are the key elements to patients' recovery of a prehabilitation or posthabilitation program as well as to establish which patients could benefit most of the aforementioned programs. Additionally, it will identify those areas of knowledge that need further study.

ANNEX 1 CASE REPORT FORM

FRAilty incidence in surGIcal European patients

European prospective cohort study of the prevalence of frailty in surgical patients.

Identifier	
HOSPITAL	
SUBJECT	
INVESTIGATOR	

CASE REPORT FORM (CRF)
Version 1.0 Date 25-February-2019

CONFIDENTIAL

DEMOGRAPHIC DATA			
Age (years)		Height (cm)	
Sex	□ Male □ Female	Weight (kg)	
Date of admission		BMI (kg/m^2)	
Date of hospital discharge		Date of surgery	
Date of consent		Date of randomization	

Inclusion criteria	**YES**	**NO**
18 years or older	□	□
Emergency or elective surgery under general anesthesia	□	□
Signature of informed consent to participate in the study	□	□

Exclusion criteria	**YES**	**NO**
Outpatient surgery	□	□
Obstetric analgesia or anesthesia	□	□
Organ transplant surgery	□	□
Cardiac surgery	□	□
Neurosurgery	□	□
Any surgery with locoregional anesthesia without general anesthesia	□	□

NOTE: Once inclusion criteria are met, informed consent must be obtained before the start of the study.

Planned surgery	
Type of procedure:	
□ Elective	□ Emergency
Type of surgery (select the closest option)	
□Abdominal	□ Thoracic
□ Neurosurgery	□ Urologic
□ Gynecologic/Obstetric?	□ Trauma-Orthopedics
□ Vascular	□ Other
Type of Anesthesia	
□ General	□ Loco-regional
Oncologic surgery?	
□ Yes □ No	

BASELINE DATA		
Clinical background	**YES**	**NO**
blood pressure hypertension	□	□
Ischaemic heart disease	□	□
Diabetes mellitus type I	□	□
Diabetes mellitus type II	□	□
Smoker	□	□
Former smoker (≥ 3 months)	□	□
Alcohol consumption (more than two drinks per day)	□	□
Dyslipidemia	□	□
COPD (Chronic obstructive pulmonary disease)	□	□
Obstructive sleep apnea	□	□
Kidney failure (definition?)	□	□
Hepatic failure (definition?)	□	□
Previous treatment	**YES**	**NO**
Antibiotics during the previous 3 months	□	□
Blood pressure medications	□	□
Aspirin	□	□
Statins	□	□
Oral antidiabetic drugs	□	□
Insulin	□	□
Inhalers	□	□
Corticosteroids	□	□
Benzodiazepines	□	□
Opioids	□	□
Chemotherapy before surgery	□	□
Radiotherapy before surgery	□	□

PREHABILITATIÓN		
The intervention consists of a full-body physical exercise program. The evidence based protocol aims to improve the functionality of patients with or without frailty. The program may be performed at home or at the hospital on an outpatient basis for at least 4 weeks.	**YES**	**NO**
Physical exercise program	□	□
Nutritional education/ protein supplements / parenteral-enteral nutrition	□	□
Cognitive training	□	□

CLINCAL FRAILTY SCALE – Before surgery		
Very fit	Robust, active, energetic, motivated. Exercise regularly.	□
Well	No active disease symptoms. Exercise or very active occasionally.	□
Managing well	Well controlled medical problems. Not regularly active (walking).	□
Vulnerable	Symptoms limit activities, but not dependent on others for daily help.	□
Mildly frail	Evident slowing and need help in instrumental activities of daily living (controlling medication, finances, transportation, heavy housework). Typically impairs shopping, walking outside alone, meal preparation and housework.	□
Moderately frail	Need help with all outside activities and housekeeping. Often have problems with stairs and need help with bathing and getting dressed.	□
Severely frail	Completely dependent for personal care, any physical or cognitive activity. Stable, not at high risk of dying within 6 months.	□
Very severely frail	Completely dependent, approaching the end of life. Typically, they could not recover from a minor illness.	□
Terminally ill	Approaching the end of life. Life expectancy < 6 months.	□

FRAIL QUESTIONNAIRE – Before surgery		
Affirmative response. 1-2 = Pre-frail; ≥3 = frail	**YES**	**NO**
Are you tired?	□	□
Are you unable to climb one flight of stairs?	□	□
Are you unable to walk one block?	□	□
Do you have more than 5 illnesses?	□	□
Have you lost 5% or more of your weight in the last 6 months?	□	□

BARTHEL INDEX – Before surgery			
Activity	Description	Score	
Feeding	1. Unable	0	☐
	2. Needs help cutting, spreading butter, etc.	5	☐
	3. Independent	10	☐
Transfers	1. Unable, no sitting balance	0	☐
	2. Major help, can sit	5	☐
	3. Minor help	10	☐
	4. Independent	15	☐
Grooming	1. Needs help with personal care	0	☐
	2. Independent face/hair/teeth/shaving	5	☐
Toilet use	1. Dependent	0	☐
	2. Needs some help, but can do something alone	5	☐
	3. Independent	10	☐
Bathing	1. Dependent	0	☐
	2. Independent	5	☐
Mobility	1. Immobile	0	☐
	2. Wheelchair independent	5	☐
	3. Walks with help of one person (verbal or physical)	10	☐
	4. Independent at least 50m (but may use aid)	15	☐
Stairs	1. Unable	0	☐
	2. Needs help (verbal or physical)	5	☐
	3. Independent up and down	10	☐
Dressing	1. Dependent	0	☐
	2. Needs help, but can do half unaided	5	☐
	3. Independent	10	☐
Bowel	1. Incontinent	0	☐
	2. Occasional accident (once/week)	5	☐
	3. Continent	10	☐
Bladder	1. Incontinent or catheterized	0	☐
	2. Occasional accident (once/day)	5	☐
	3. Continent	10	☐

CHARLSON INDEX- Before surgery							
Weight	**Condition**	**YES**	**NO**	**Weight**	**Condition**	**YES**	**NO**
1	Myocardial infarction	☐	☐	1	Liver disease, mild	☐	☐
1	Peripheral vascular disease	☐	☐	2	Cerebrovascular disease + disability	☐	☐
1	Dementia	☐	☐	2	Renal disease, AKI II-III	☐	☐
1	Chronic pulmonary disease	☐	☐	2	Diabetes with end organ damage	☐	☐
1	Ulcer disease	☐	☐	2	Cancer	☐	☐
1	Diabetes Mellitus	☐	☐	3	Liver disease, moderate or severe	☐	☐
1	Cerebrovascular disease	☐	☐	6	AIDS	☐	☐
1	Connective tissue disease	☐	☐	6	Metastatic malignancy	☐	☐

Cognitive evaluation (Short Blessed Test) – Before surgery						
ITEM	**Test**	**Correct**	**Incorrect**	**Weight**	**Number of mistakes 0-5**	**Total**
1	What year are we in?	□	□	X4		
2	What month are we in?	□	□	X3		
3	Repeat the name and address: John Wayne, 3th avenue London	□	□	-		
4	What time is it?	□	□	X3		
5	Count back from 20 to 0	□	□	X2		
6	Count back the months of the year	□	□	X2		
7	Repeat the name and address: John Wayne, 3th avenue London	□	□	X2		
	Punctuation (0-28)					

EuroQOL-5D— Before surgery

Mobility		**Pain/Discomfort**	
I have no problems in walking about	□	I have no pain or discomfort	□
I have some problems in walking about	□	I have moderate pain or discomfort	□
I am confined to bed	□	I have extreme pain or discomfort	□
Self-care		**Anxiety/depression**	
I have no problems	□	I am not anxious or depressed	□
I have some problems washing or getting dressed	□	I am moderately anxious or depressed	□
I am unable to wash or dress myself	□	I am extremely anxious or depressed	□
Usual activities			
I have no problems performing my usual activities	□		
I have some problems performing my usual activities	□		
I am unable to perform my usual activities	□		

INTRAOPERATIVE DATA	YES	NO
Transfusion of blood components	☐	☐
Vasoactive drugs	☐	☐
Anesthetic depth monitoring	☐	☐
PERIOPERATIVE DATA		
Duration of surgery		min
Duration of mechanical ventilation (until extubation)		min

POSTOPERATIVE DATA	YES	Hours	NO
Admission to Post-Anesthesia Care Unit (PACU)	☐		☐
Planned ICU admission	☐		☐
Unplanned ICU admission	☐		☐
ICU readmission	☐		☐
Surgical reintervention when? During PACU stay?	☐		☐
Hospital readmission (first 30 days)	☐		☐

POSTOPERATIVE DATA. Care bundles.	YES	Hours*	NO
Active mobilization			
Sitting on the bed	☐		☐
Sitting on a chair	☐		☐
Sitting	☐		☐
Walking	☐		☐
Nutrition			
Enteral	☐		☐
Parenteral	☐		☐
Oral liquids	☐		☐
Oral solid	☐		☐
Delirium screening	☐		☐
Cognitive dysfunction screening	☐		☐

***Hours since begins from the end of surgery. For delirium and cognitive dysfunction screening, the days after surgery when it is performed must be indicated.**

POSTOPERATIVE OUTCOMES			
Postoperative complications			
Does the patient have any complications 30 days after surgery?			
□ Yes □ No			
If the answer is yes, indicate the cause:			
□ Acute respiratory failure		□ Reintubation	
□ COPD exacerbation		□ ARDS	
□ Surgical wound infection		□ Pneumonia	
□ New onset atrial fibrillation		□ Acute pulmonary edema	
□ Myocardial ischemia		□ Acute kidney failure(KDIGO II-III)	
□ Septic shock		□ Sepsis	
□ Delirium		□ Cognitive dysfunction	
□ Paralytic ileus		□ Other (specify):	
Clavien-Dindo classification (for the most serious complication):			
□ Grade I	□ Grade II	□ Grade III	□ Grade IV

CLINCAL FRAILTY SCALE – 30 days after surgery		
Very fit	Robust, active, energetic, motivated. Exercise regularly.	□
Well	No active disease symptoms. Exercise or very active occasionally.	□
Managing well	Well controlled medical problems. Not regularly active (walking).	□
Vulnerable	Symptoms limit activities, but not dependent on others for daily help.	□
Mildly frail	Evident slowing and need help in instrumental activities of daily living (controlling medication, finances, transportation, heavy housework). Typically impairs shopping, walking outside alone, meal preparation and housework.	□
Moderately frail	Need help with all outside activities and housekeeping. Often have problems with stairs and need help with bathing and getting dressed.	□
Severely frail	Completely dependent for personal care, any physical or cognitive activity. Stable, not at high risk of dying within 6 months.	□
Very severely frail	Completely dependent, approaching the end of life. Typically, they could not recover from a minor illness.	□
Terminally ill	Approaching the end of life. Life expectancy < 6 months.	□

FRAIL QUESTIONNAIRE – 30 days after surgery		
Affirmative response. 1-2 = Pre-frail; ≥3 = frail	**YES**	**NO**
Are you tired?	□	□
Are you unable to climb one flight of stairs?	□	□
Are you unable to walk one block?	□	□
Do you have more than 5 illnesses?	□	□
Have you lost 5% or more of your weight in the last 6 months?	□	□

BARTHEL INDEX – 30 days after surgery			
Activity	Description	Score	
Feeding	4. Unable	0	□
	5. Needs help cutting, spreading butter, etc.	5	□
	6. Independent	10	□
Transfers	5. Unable, no sitting balance	0	□
	6. Major help, can sit	5	□
	7. Minor help	10	□
	8. Independent	15	□
Grooming	3. Needs help with personal care	0	□
	4. Independent face/hair/teeth/shaving	5	□
Toilet use	4. Dependent	0	□
	5. Needs some help, but can do something alone	5	□
	6. Independent	10	□
Bathing	3. Dependent	0	□
	4. Independent	5	□
Mobility	5. Immobile	0	□
	6. Wheelchair independent	5	□
	7. Walks with help of one person (verbal or physical)	10	□
	8. Independent at least 50m (but may use aid)	15	□
Stairs	4. Unable	0	□
	5. Needs help (verbal or physical)	5	□
	6. Independent up and down	10	□
Dressing	4. Dependent	0	□
	5. Needs help, but can do half unaided	5	□
	6. Independent	10	□
Bowel	4. Incontinent	0	□
	5. Occasional accident (once/week)	5	□
	6. Continent	10	□
Bladder	4. Incontinent or catheterized	0	□
	5. Occasional accident (once/day)	5	□
	6. Continent	10	□

Cognitive evaluation (Short Blessed Test) – 30 days after surgery						
ITEM	**Test**	**Correct**	**Incorrect**	**Weight**	**Number of mistakes 0-5**	**Total**
1	What year are we in?	□	□	X4		
2	What month are we in?	□	□	X3		
3	Repeat the name and address: John Wayne, 3th avenue London	□	□	-		
4	What time is it?	□	□	X3		
5	Count back from 20 to 0	□	□	X2		
6	Count back the months of the year	□	□	X2		
7	Repeat the name and address: John Wayne, 3th avenue London	□	□	X2		
	Punctuation (0-28)					

EuroQOL-5D— 30 days after surgery			
Mobility		**Pain/Discomfort**	
I have no problems in walking about	□	I have no pain or discomfort	□
I have some problems in walking about	□	I have moderate pain or discomfort	□
I am confined to bed	□	I have extreme pain or discomfort	□
Self-care		**Anxiety/depression**	
I have no problems	□	I am not anxious or depressed	□
I have some problems washing or getting dressed	□	I am moderately anxious or depressed	□
I am unable to wash or dress myself	□	I am extremely anxious or depressed	□
Usual activities			
I have no problems performing my usual activities	□		
I have some problems performing my usual activities	□		
I am unable to perform my usual activities	□		

Survival	Alive	Dead
At hospital discharge	□	□
30 days after surgery	□	□

Observations

ADMINISTRATIVE DATA		
	YES	**NO**
Extended ICU visit (> 10h)	□	□
Physiotherapist in ICU	□	□
Nutritionist in ICU	□	□
Nurse ratio in ICU > 1/2	□	□
Nurse ratio in PACU > 1/4	□	□
Nurse ratio in ward > 1/8	□	□

Was the patient excluded from the study?

□ Yes □ No

If the answer is yes, indicate the cause:

□ Patient withdraws consent

□ Surgery was not performed

□ Patient meets exclusion criteria

□ Other (specify):

Signature: Name and surnames: Date:

NOTE: At the end of the study, a paper copy of the completed CRF signed by the investigator will be collected

ANNEX 2. Definition of complications

These definitions are based on those proposed by the European Society of Anesthesiology (ESA) and the European Society of Intensive Care Medicine (ESICM).

Jammer Ib, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions. A statement from de ESA-ESCIM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015; 32:88-105.

Complicación	Definición	Escala de gravedad
Acute Kidney Injury	Mild: Serum creatinine Increase of 1.5-1.9 times baseline value within 7 days or ≥0.3mg/dL (30 µmol/L) within 48 hours. Urine output ≤0.5ml/kg/h for 6-12 hours Moderate: Serum creatinine Increase of 2.0-2.9 times baseline value within 7 days. Urine output ≤0.5 ml/kg/h for 12 hours. Severe : Serum creatinine Increase of 3.0 times baseline within 7 days or increase in serum creatinine to ≥4.0 mg/dL (≥350 µmol/L) with an acute rise of >0.5 mg/dL (>50 µmol/L) or initiation of renal replacement therapy. Urine output ≤0.3 ml/kg/h for 24 hours or Anuria for 12 hours.	Included in the definition
Acute Respiratory Distress Syndrome (ARDS)	Respiratory failure, or new or worsening respiratory symptoms, commencing within one week of surgery; and a chest radiograph or computed tomography scan which demonstrates bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; and respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present.	Mild: PaO2:FiO2 between 200 and 300 mmHg with PEEP or CPAP ≥5 cmH2O Moderate:PaO2:FiO2 between 100 and 200 mmHg with PEEP ≥5 cmH2O Severe: PaO2:FiO2 ≤100 mmHg with PEEP ≥5 cmH2O
Pneumonia	Chest radiographs with new or progressive and persistent infiltrates, or consolidation, or cavitation, and at least one of the following: a)Fever (>38°C) with no other recognized cause b)Leucopaenia (<4,000 white blood cells/mm3) or leucocytosis (>12,000 white blood cells/mm3) c)For adults >70 years old, altered mental status with no other recognised cause …and at least two of the following: New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or permanent functional limitation or death. It almost always

	New onset or worsening cough, or dyspnoea, or tachypnoea Râles or bronchial breath sounds Worsening gas exchange (hypoxia, increased oxygen or ventilator demand)	requires clinical treatment.
Cardiac arrest	The cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. ECG changes may corroborate the incidence of cardiac arrest.	Severity grading: None, yes or no
Arrhythmia	Electrocardiograph (ECG) evidence of cardiac rhythm disturbance.	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or permanent functional limitation or death. It almost always requires clinical treatment.
Deep Venous Thrombosis	Un nuevo coágulo de sangre o trombo dentro del sistema venoso. Se requiere un examen sistemático en los ensayos en los que la TVP es una medida de resultado importante. Las pruebas diagnósticas apropiadas incluyen ecografía, venografía, tomografía computarizada o resonancia magnética	
Stroke	Embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory	
Pulmonary oedema	Evidence of fluid accumulation in the alveoli due to poor cardiac function.	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or permanent functional limitation or death. It almost always requires clinical treatment.
Pulmonary embolism (PE)	A new blood clot or thrombus within the pulmonary arterial system. Guidance: Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D- dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.	
Surgical site infection (superficial)	Infection involving only superficial surgical incision which meets the following criteria: 1)Infection occurs within 30 days after surgery and 2)Involves only skin and sub-cutaneous tissues of the incision and 3)The patient has at least one of the following:	

	a) Purulent drainage from the superficial incision b) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision and at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, or superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture- negative finding does not meet this criterion. c) Diagnosis of a incisional surgical site infection by a surgeon or attending physician	
Surgical site infection (deep)	An infection which involves both superficial and deep parts of surgical incision and meets the following criteria: 1) Infection occurs within 30 days after surgery if no surgical implant is left in place or one year if an implant is in place and 2) The infection appears to be related to the surgical procedure and involves deep soft tissues of the incision (e.g. fascial and muscle layers) and 3) The patient has at least one of the following: a) Purulent drainage from the deep incision but not from the organ/space component of the surgical site b) A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or no cultures were taken whilst the patient has at least one of the following signs or symptoms of infection: fever (>38°C) or localized pain or tenderness. A culture-negative finding does not meet this criterion. c) An abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination d) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or permanent functional limitation or death. It almost always requires clinical treatment.
Surgical site infection	An infection which involves any part of the body excluding the fascia or muscle layers and meets the following criteria: 1) Infection occurs within 30 days	

(organ/space)	after surgery and 2) The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and 3) The patient has at least one of the following: a) Purulent drainage from a drain that is placed through a stab wound into the organ/space b) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space c) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination d) Diagnosis of an organ/space surgical site infection by a surgeon or attending physician	
Bloodstream infection	An infection which is not related to infection at another site and which meets either of the following criteria: 1)Patient has a recognised pathogen cultured from blood cultures which is not related to an infection at another site 2)Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following: a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and a physician starts antimicrobial therapy c) Positive blood antigen test	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or
Myocardial infarction	Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: - Symptoms of ischaemia - New or presumed new ST-segment or T-wave ECG	

	changes or new left bundle branch block - Development of pathological Q-waves on ECG - Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality - Identification of an intra-coronary thrombus at angiography or autopsy	permanent functional limitation or death. It almost always requires clinical treatment.
Urinary tract infection	An infection associated with at least one of the following signs or symptoms which should be identified within a 24 hour period: Fever (>38 °C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause and a positive urine culture of ≥105 colony forming units/mL with no more than two species of microorganisms	
Paralytic ileus	Failure to tolerate solid food or defecate for three or more days after surgery	*Mild*: it produces only temporary damage and generally does not require a specific clinical treatment. *Moderate*: more serious complication, but usually does not cause permanent damage or functional limitation. It usually requires clinical treatment *Serious*: it produces a significant prolongation of the hospital stay and / or permanent functional limitation or death. It almost always requires clinical treatment.
Delirium	Delirium may be identified using the Intensive Care Delirium Screening Checklist. Patients are first evaluated for an altered level of consciousness. Those with a response to mild or moderate stimulation, an exaggerated response to stimulation or normal wakefulness are evaluated fully. Patients receive one point for each of the following criteria: inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance or symptom fluctuation.	Included in the definition
Post-operative haemorrhage	Blood loss occurring within 72 hours after the end of surgery which would normally result in transfusion of blood. Gastro-intestinal bleeding is defined above.	*Mild*: Any sign of hemorrhage (any bleeding that is more than expected, including bleeding that was only identified in an

		imaging study), that does not meet the criteria for the moderate-severe type, but requires at least one of the following points: • Non-surgical medical intervention by a health professional (examples include stopping antiplatelet therapy, antithrombotic medications, compression at the bleeding site, use of drugs to reverse the anticoagulant effect, such as: protamine and vitamin k). • Requires hospitalization or higher level of care. • Requires rapid evaluation with tests such as: blood count, urinalysis, coagulation tests, endoscopy and tomography. *Moderate*: • Bleeding with a decrease in hemoglobin from ≥ 3 to <5 g / dl (related to bleeding). • Any need for transfusion due to obvious bleeding. • Decrease in hemoglobin ≥ 5 g / dl (related to bleeding). • Bleeding that requires surgical intervention to control it. • Bleeding that requires the use of vasoactive agents . *Severe*: Transfusion of ≥ 5 units of red blood cells, in a period of 48 hours. Fatal bleeding.

ANNEX 3: WORK PLAN

TASK	RESPONSIBLE	TIMELINE	COMMENTS
Funding	Steering Committee		Grant application.
Protocol drafting	Steering Committee	Complete	
Registration of the study	Steering Committee		It will be registered in clinicaltrials.org
Recruitment of data collectors	Steering Committee Coordinators	It will start immediately after raising funding. Therefore it is foreseen that regional coordinators will be selected simultaneously at the study enrollment.	Expected time: 3 months.
National Ethics Committee	Steering Committee	After raising funding. Expected time: 2 months.	
Protocol publication	Steering Committee	Immediately after the approval by the Ethics Committee. The participation of an external editorial manager is foreseen in order to ensure full transparency.	The protocol will be published in GERM, Red GERM.
National, communities and local coordinators selection	Steering Committee	It will start immediately after raising funding. Therefore it is foreseen that national, communities and local coordinators will be selected simultaneously at the study enrollment.	Coordinators will be selected based on their prior experience in studies' participation*. Coordinators will select local coordinators.
Problem-solving	Communities coordinators	2 months	

Start of the study	Steering Committee Coordinators Participant centres	One month per hospital, one month of follow-up. The participant centres will have the option to perform the intervention during 5 months.	Expected time: 6 months.
Data analysis	Steering Committee	1 month	
Composition of the manuscript	Steering Committee Drafting Committee	1 month	
Manuscript reviewing	Editorial Manager	1 month	
Manuscript publication	Steering Committee	(it is not possible to foresee a date)	

ANNEX 4. INFORMATION TO PATIENTS

Ethics Committee Approval Number:

STUDY INFORMATION SHEET FOR PATIENTS AND CONSENT FORM

STUDY INFORMATION SHEET FOR PATIENTS

(VERSION 1.0, February 2019)
Number of approval by the Ethics Committee:

Name of the study: FRAilty incidence in surGIcal European patients **(FRAGILE). European prospective cohort study of the prevalence of frailty in surgical patients.**

Dear patient,
You have been invited to participate in a research study. We would like to explain to you why this study is being conducted and what it will entail for you. Please take the time to carefully read the following information and discuss it with other people, if you wish. Please ask us if something is unclear or if you need more information. Take your time to decide if you want to participate. Your participation is important to obtain the knowledge we need, but before making a decision you must:
- Read this entire document
- Understand the information contained in the document
- Ask all the questions you consider necessary
- Consult with your doctor-trusted person
- Make a thoughtful decision
- Sign the informed consent, if you finally want to participate.

If you decide to participate, you will be given a copy of this document and signed consent. Please keep them in case you need it in the future.

Why are you asked to participate?
You have been invited to participate in this study, because you must undergo surgery. The FRAGILE is an international observational study, with the participation of centres worldwide. This means that routine clinical practice will not change, and no additional or alternative treatment will be performed. Instead, data of routine clinical practice will be collected.

What is the purpose of this study?
Our main objective is to carry out an observational study to determine the prevalence of frailty in the surgical patient, and its possible relation with postoperative outcomes like quality of life and hospital length of stay. We also aim to assess which measures that could potentially improve the prognosis of frail patients are being adopted at the present time, and the relation between these measures and patient clinical outcomes. Several studies show a direct association between frailty and a slowing-down in patient recovery, a non-recovery of the preoperative status and even a higher risk of mortality than non-frail patients.

What do I have to do if I decide to participate?
Remember that your participation is voluntary and if you decide not to participate this will not affect your attendance or your relationship with the researcher. If you decide to participate, the researchers will collect preoperative data derived from the pre-anesthesia consultation, as well as data on the surgical intervention and postoperative data. Always so that these data remain anonymous. Given that this is an observational study, no additional intervention will be made to those that are performed regularly in your center. Neither will any extraordinary test be performed, and of course, planned tests will not be dispensed with.
It is not required that you make more visits to the hospital, either before or after the surgery. Sólo le llamaremos por teléfono a los 30 días de la intervención quirúrgica para evaluar su estado de salud.

Do I have an obligation to participate?
No, your participation is completely voluntary. If you decide to participate, please sign the consent form to show that you agree to participate and keep the copy that is delivered with this information sheet. If you decide not to participate in the study, your decision will not affect your treatment or the care you are receiving at this time or that you will receive in the future.

Will I get any benefit for participating?
Being a research study aimed at generating knowledge, it is not expected that you will obtain direct benefit by participating or will receive any financial compensation for it, although you will contribute to the advancement of knowledge and social benefit.

What risks or inconveniences does it have to participate?
FRAGILE is an observational study, therefore your treatment will not change because you participate in this study. Perioperative treatment (before, during and after your surgery) will be prescribed according to the healthcare practice and your needs as a patient and will not be altered by the inclusion in the study.

Risk for confidentiality
The clinical information obtained in this project will be stored in a database protected by current legislation, under the responsibility of the responsible institutions' investigators. These anonymized data will be kept for future studies, unless you indicate otherwise. The results of this research can be disseminated in journals, medical databases and scientific forums. Personal data that could identify you will never be revealed. The investigators will always have a duty to protect your privacy and maintain all your information confidentially.

Privacy and use of clinical information
The treatment, communication and transfer of your data will be performed according the Regulation (EU) 2016/679 of the European Parliament and the April 27th 2016 Council on Data protection (RGPD). The principal investigators, Dr Carlos Ferrando and Dr César Aldecoa, will be accountable for the custody of the participants' identification codes. As a participant, you may exercise your rights of access, rectification, objection and/or deletion, by contacting any of the principal investigators (telephone numbers provided at the end of this document). Moreover, you can restrict processing of incorrect data, request a copy of your data or request
the transfer of your data to a third party (portability). You may exercise your rights by contacting the principal investigators of the study [Carlos Ferrando (cafeoranestesia@gmail.com), César Aldecoa (cesar.aldecoa@gmail.com)]. We remind you that data cannot be delated even though you cease to take

part in the study, in order to guarantee the study's validity and to comply with the legal and medicinal products requirements for authorisation. You are entitled to contact the Data Protection Agency if not satisfied. Both the Centre and the Promoter are responsible for data treatment and they commit to meet the data protection regulations in force. Data collected for the study will be identified with a code, so that no information that could identify you is not included. Only your doctor and collaborators will be able to relate your data with you and your clinical history. Therefore, your identity will not be revealed to anyone, except for the healthcare authorities whenever required or in cases of medical emergency. Ethical Committees, healthcare authorities' representatives and authorised personnel will only have access to data in order to perform checks on personal data, on the study procedures and on the compliance with the Good Clinical Practice Standards (always maintaining confidentiality).
The principal investigator and the promoter are obliged to keep all the data collected throughout the study for at least 25 years after the end of the study. After that, your personal data will only be stored at your hospital for your health care. In case we transfer your encoded data outside the EU, to scientific researchers or service providers that collaborate with us, your data will be safeguarded by contracts or other mechanisms recommended by data protection authorities. Further information can be obtained by contacting the Data Protection Delegate (Carlos Ferrando Ortolá, cafeoranestesia@gmail.com).

Withdrawal from the study
Even though you have agreed to participate, you may leave the study whenever you wish without any effect on your medical care and without having to offer any explanation. All you need to do is express your intention to the study's principal investigator or his collaborators. If you decide to withdraw from the study, no further data will be collected, while already collected data will be filed.

How can I know the results of the study?
You have the right to know the results of this study, both the general results and those derived from your specific data. You also have the right not to know these results if you wish. For this reason, in the informed consent document, we will ask you which option you prefer. In case you want to know the results, the researcher will send you the results. The overall results of this study will be sent to medical and scientific publications and presented at meetings in the same field for dissemination. The FRAGILE website (www.grupogerm.es) will also provide study data and updated recruitment information, both for patients and for the general public.

¿What if I have any questions during my participation in the?
In case you have any question or doubt regarding your participation, you can contact the principal investigators at Hospital Clínic de Barcelona (Carlos Ferrando, Chief of the surgical ICU) o at Hospital Río Hortega de Valladolid (César Aldecoa, Chief of the Anesthesiology department), during working hours (08:000-15:00) or by email to the aforementioned addresses.

Who is organizing and funding this research?
This study is being carried out by a network of doctors from all over the world. The study is coordinated by Dr. Carlos Ferrando and Dr César Aldecoa. The study is funded by the Spanish Group of Multimodal Rehabilitation (GERM).

Are there economic interests in this study?
Researchers will not receive specific retribution for the dedication to the study (in addition to their usual salary as researchers or doctors). You will not be rewarded for participating. There is no possibility of this study generating benefits in the form of patents.

Who has reviewed this study?
This research study has been reviewed by an independent group of people from a Research Ethics Committee, to protect your safety, your rights, your well-being and your dignity. The Healthcare Ethics Committee of the Hospital Clínic y Provincial de Barcelona has reviewed the study and has given the approval to carry it out.

What am I supposed to do now?
You must decide if you want to participate in this study. Please, think about what participating in the study involves and talk with your friends and family. The research doctor and the nurse will be happy to answer any questions you may have. When you decide, please inform your doctor. You will be asked to sign a consent form and you will be given a copy that you must keep attached to this information sheet. Please keep these documents. If at any time you have any questions about the study, you can contact the researchers of the FRAGILE study, whose contact information is indicated at the end.

Who can give me more information?
For further information, do not hesitate to contact:
Carlos Ferrando
Telephone number: 609892732
E-mail address: cafeoranestesia@gmail.com

César Aldecoa
Telephone number: 657500031
E-mail address: cesar.aldecoa@gmail.com

CONSENT FORM

Study Title:

FRAilty incidence in surGIcal European patients (FRAGILE)

European propective cohort of the prevalence of frailty in surgical patients.

I, ... (name and surname of the participant) with ID card……, confirm that:
I have read and understood the information sheet that has been provided.
I have had the opportunity to ask questions and I have received satisfactory answers.

I have talked to :.....(name of the researcher)
I understand that my participation is voluntary.
I understand that I am free to withdraw from the study:
1) at any time
2) without giving any reason
3) without my medical care being affected.

I hearby agree to take part in the study.
Do I want to be informed about the results of the study: yes no (check what applies).
I agree that my medical data may be looked at by individuals from the FRAGILE Team and I am aware that this consent may be withdrawn at any time. Doy mi conformidad para que el equipo investigador me pueda llamar por teléfono a los 30 días de la cirugía
I have recieved a signed copy of this Consent Form.

Signature of the patient:

Date:

I have explained the study and its purpose to the patient.
Signature of the researcher:

Date:

ORAL WITNESSED CONSENT FORM

The declaration of the impartial witness is compulsory when the patient, the father or mother of the patient or the legal representative are incapable of reading or writing.

Study Title:

FRAilty incidence in surGIcal European patients (FRAGILE)

European prospective cohort of the prevalence of frailty in surgical patients.

I, ... (name and surname of the participant) with ID card……, confirm that:
I have received the information sheet.
I have had the opportunity to ask questions and I have received satisfactory answers.
I have been provided with adequate information about the study.

I have talked to :.....(name of the researcher)
I hereby declare, under my own responsibility, that: …… (name of the participant) with ID card ……:
Understands that his/her participation is voluntary.
Understands that he/she is free to withdraw from the study:
1) at any time
2) without giving any reason
3) without my medical care being affected.
Has freely expressed his/her agreement to participate in the study.

Signature of the witness Signature of the researcher

Date Date

LEGAL REPRESENTATIVE CONSENT FORM

Study Title:

FRAilty incidence in surGIcal European patients (FRAGILE)

European prospective cohort of the prevalence of frailty in surgical patients.

I, ... (name and surname of the legal representative) with ID card…… and as …….. confirm that:
I have read and understood the information sheet that has been provided .
I have had the opportunity to ask questions and I have received satisfactory answers.
I have been provided with adequate information about the study.

I have talked to :..... (name of the researcher)
I understand that the participation in the study is voluntary.
I understand that it is possible to withdraw from the study:

1) whenever the participant may want to.
2) without giving any reason
3) without the medical care being affected.

In my presence, it has been given to …….. (name of the participant) all the necessary information adapted to his/her level of understanding and agrees to participate in the study.
I hereby agree to …… (name of the participant) participating in the study.

Signature of the legal representative

Signature of the researcher

Date

Date

ANNEX 5 – DATA PROTECTION

1. *Electronic database*

The electronic database and eCRF platform are hosted by Castor EDC, a Netherlands based company which works with certified servers compliant with relevant certifications (ISO27001, ISO9001) and/or national or international standards (HIPAA, NEN7510). Castor EDC complies with all applicable laws and regulations: good clinical practice (GCP), 21 CFR Part 11, annexed 11 of the European Union and UE and the European Directive on data protection.

In the study different people have been assined different rights of access. Access to the database by any roles is password protected.

- Local hospital staff, have access to the eCRF and access to the data entered from patients from their own hospital. Entered data is checked and approved by the local PI.
- Study Coordinators and Data Managers, have access to the data from all hospitals.
- Chief Investigators have access to the data from all hospitals in order to perform data cleaning.

2. *Data ownership*

Grupo Español de Rehabilitación Multimodal (GERM) is the owner of the aggregated data. Local PIs are owner of the data that originates from their local site.

3. *Data (pseudo)-anonymity*

The data entered in the database, Castor EDC, cannot contain any information rendering the patient identifiable. As a consequence, the data present in the database has been pseudonymised by the hospital Staff. This implies that all the data that GERM receives is pseudonymised. Chief Investigators and Data Managers do not have access to the identity of the patients entered. All handling of personal data will comply with the GCP Guidelines and follow strictly the legal and national requirements of GDPR.

4. *Is there any chance that patient data can be exchanged with countries outside the EEC?*

Yes, if requests for the data are made from outside the EEC it is possible that the data are sent outside the EEC. However, further processing will be allowed only in the context of scientific research and GERM will ensure that the recipients have implemented organisational and technical safeguards.

5. *Data Processing Agreements (DPAs) and Data Transfer Agreements (DTAs)*

FRAGILE is an observational study. GERM and hospitals can be considered both as controllers of the data. As a consequence, no DPA has to be put into place.

Inside Europe
If a DPA is needed based on local legislation, please contact us a fragile@grupogerm.es. Please coordinate with the National Coordinator for a nationally adapted template.

Outside Europe
A Data Transfer Agreement (DTA) can be put into place in countries outside Europe when requested. Please contact us at fragile@grupogerm.es.

6. *Archiving, further processing and sub-studies*

After the end of the study, GERM will store the data for 25 years, according to Spanish Legislation in Clinical Trials. You are authorized to store your data accordingly to your country's legislation.

The local investigator is entitled to receive its centre's data upon request, after the publication of the main paper of the study. If you want to do a sub-study, please contact the Chief Investigators with your written and expressed request. Your demand will be analysed by the Steering Committee. If your project is approved, you will receive the data.

ANNEX 6- AUTHORSHIP POLICY

We, as the study steering committee, as fully aware that authorship is a major motivating factor in centres participating. We intend to have an inclusive authorship policy.

This publication charter is based on recommendations of the International Committee of Medical Editors (http://www.icmje.org/icmje-recommendations.pdf). As recommended by the International Committee of Medical Journal Editors (ICMJE), authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, and submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

'The FRAGILE Study Group'

The principal FRAGILE paper will be published on behalf of all contributors. The author will be listed as 'The FRAGILE Study Group' and a footnote will carry the names and affiliations of contributors. Individual contributors will be included in this list if they registered as local investigators on the FRAGILE data entry website and have a certificate of participation, or they are a member of the core study management team

If you've significantly contributed towards the conduct of FRAGILE then we want to recognise your work and include you in 'The FRAGILE Study Group'. Until the study analysis is complete, we won't have decided the destination journal and the interpretation of the ICJME rules on authorship varies between journals. It would clearly be impractical to seek approval of the final version to be published AND agreement to be accountable for all aspects of the work for all members of 'The FRAGILE Study Group', this will be performed by the Writing Committee.

There is precedent with projects that have resulted in publications with hundreds or thousands of authors. For example, when EuSOS was published in the Lancet in 2012 (https://www.ncbi.nlm.nih.gov/pubmed/22998715) with almost 2000 authors. Or an analysis from ISOS published in Intensive Care Medicine (https://www.ncbi.nlm.nih.gov/pubmed/28439646) with over 2000 authors. However, similar publications in other journals, like the British Journal of Anaesthesia (https://www.ncbi.nlm.nih.gov/pubmed/27799174) or the European Journal of Anaesthesiology (https://www.ncbi.nlm.nih.gov/pubmed/28633157) list collaborators, rather than authors. Whether acknowledged as authors or collaborators, we will endeavour to ensure that everyone is acknowledged and incorporated into the MEDLINE database to ensure that PUBMED

searches identify their efforts.

What do you mean 'significantly contributed'?

1. The national co-ordinators (NC) will be included.
2. Everyone on the Study Steering Committee (SSC) and Writing Committee will be included. The Writing committee will largely be comprised of the SSC
3. For each centre that recruits a reasonable number of patients* and has satisfactory data quality we will include the principal investigator and co-investigators.

   We are deliberately not giving specific numbers for 'reasonable' and 'large' as experience from other similar studies suggests that this becomes seen as a target rather than a minimum. Equally important to the numbers of recruits are the completeness of the data and its quality. The SSC with the ESA office will adjudicate on these matters.

Manuscripts

The results of FRAGILE and its sub-studies will be published in peer–reviewed international medical journals and presented at International and national meetings. We anticipate more than one manuscript:

- Main manuscript : All members of 'The FRAGILE Study Group' will be acknowledged in this manuscript.
- Additional manuscripts. Equally, all members of 'The FRAGILE Study Group' will be acknowledged in these manuscripts unless they are restricted to a single country. If these manuscripts are sub analyses of combined countries, these will also *include those not recruiting to these countries*. There will be separate Writing Committees for these manuscripts, still including the SSC but with leads from countries within these regions.
- Additional analyses. We anticipate additional analyses – both determined pre-hoc (prior to analysis) and post-hoc (after analysis). The FRAGILE trial steering committee encourages high quality secondary analyses of the trial data and supports the wider principle of data sharing. FRAGILE investigators will be given priority to lead secondary analyses. Participation and authorship opportunities will be based on contribution to the primary study. No publications are allowed before the primary publication, however, if the primary manuscript has not been accepted for publication within twelve months following the completion or termination of the clinical trial at all sites, a co-ordinating investigator may publish clinical methods and data from their own site. Where necessary, a prior written agreement will set out the terms of such collaborations. Investigators should submit a secondary study proposal for review by the steering committee. The steering committee will consider the scientific validity and the possible

effect on the anonymity of participating centres prior to approval of secondary study proposals. ‘Cleaned’ data from the international dataset will only be released after the statistical analysis plan for the secondary study has been approved. Any data sharing requests/proposals must be approved by the Data Sharing Committee at the coordinating centre and will require a Data Sharing Agreement. Any analysis incorporating FRAGILE data from one or more study sites will be considered a secondary analysis and subject to these rules.

- Any NC or PI is invited to suggest analyses and take over the lead after determination by the SSC. All members of ‘The FRAGILE Study Group’ will be acknowledged in this manuscript.
- Studies that use FRAGILE as the backbone to deliver additional assessments, potentially translational or physiological.. Publications using data derived from EuroPOWER have the potential to impact the reputation of the study. Before any manuscript is submitted to a journal it must be reviewed and approved by the trial steering committee or nominated deputies. This process will occur in a timely manner. If a manuscript is rejected, constructive feedback will be given to help the authors improve the paper. These studies are encouraged by the SSC will be examined on a case by case basis
- This policy does not contradict the protocol or the FAQ but provides further detail.