**Comparison of preoperative frailty screening instruments in elective colorectal surgery: a prospective study**

**Study protocol version 3, 12-06-2020**

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# ADMINISTRATIVE INFORMATION

## Title

Comparison of preoperative frailty screening instruments in elective colorectal surgery: a prospective study.

## Trial registration

The study protocol will be registered on the ISRCTN clinical trial registry.

##  Protocol version

Study protocol version 3, 12-06-2020

##  Funding

A KOOR predoctoral 50% research mandate for Dr. Katleen Fagard (PhD student and study coordinator) has been attributed for 2 years (10/2019 – 9/2021). A research assistant will be employed by the Department of Public Health & Primary Care, Division of Gerontology and Geriatrics, KU Leuven.

## Participating centres

The study will take place in the University Hospitals (UH) Leuven. In a later stage this study might be extended to a multicentre study in Belgium, for which an amendment will be submitted to the Ethical Committee.

##  Roles and responsibilities

### 1.6.1. Applicants

Dr. Katleen Fagard1

Prof. Dr. J. Flamaing1,2

### 1.6.2. Core research team

Dr. Katleen Fagard (project manager)1

Prof. Dr. Johan Flamaing (project coordinator)1,2

Prof. Dr. Albert Wolthuis (project coordinator)3,4

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### 1.6.4. Statistical advice

Dr. Annouschka Laenen. Department of Public Health & Primary Care, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat), KU Leuven, Kapucijnenvoer 35 blok d - box 7001, 3000 Leuven, Belgium.

# INTRODUCTION

## Background and rationale

The aging of our society leads to an increasing demand for colorectal surgical procedures in older patients.1 Although surgery is often clearly indicated, risks and benefits should be carefully weighed in this patient group. After all, older patients are more likely to experience adverse postoperative outcomes, such as medical and surgical complications, prolonged hospital stays, loss of functionality, cognitive decline, or need for admission to rehabilitation or prolonged care facilities.2,3 This is largely due to the presence of age-related physiological decline in organ systems, co-morbidity and geriatric syndromes. These features can lead to frailty, which is a physiological syndrome characterized by decreased reserves and reduced resistance to stressors, resulting from cumulative declines across multiple physiologic systems leading to loss of homeostatic capacity.4,5 As the aging process varies substantially among individuals, clinical decisions should not be based on chronological age alone, but also on the basis of their biological age or frailty profile.6,7

The golden standard for assessing frailty is a comprehensive geriatric assessment. However, this is time-consuming and requires specialised skills.8,9 In the absence of time and resources, a two-step approach is preferred: first a short screening test for frailty and subsequently, in the case of positive screening, a more extensive geriatric assessment that identifies all problems for which tailored interventions could be applied.7,10,11 Two theoretical models of frailty exist: the frailty phenotype model and the deficit accumulation model.12 Based on these models, numerous frailty screening instruments have been developed that can be carried out by non-specialists in various clinical settings, including the preoperative outpatient evaluation clinic.8 Many of these screening instruments have been investigated for their predictive value for adverse postoperative outcomes and seem superior to chronological age in predicting postoperative outcomes in older patients.11,13,14 Outcome prediction is important for shared decision making and tailored patient care.11,15

To date, however, there is no consensus on which screening instrument would be most appropriate for the preoperative practice, due to lack of comparative research.6,16,17 In the colorectal surgical population, studies regarding frailty screening are scarce, and usually limited to patients with cancer.10,14 There is no generally accepted recommendation about the best way to measure frailty in surgical candidates.7,11 The prevalence of frailty in older patients undergoing elective colorectal surgery is estimated between 25 and 46%, depending on the screening instrument used to measure frailty and the methodology of the studies (recruitment, age cut-offs and other in- and exclusion criteria).10

This study is performed as part of a quality improvement project in our hospital, in which a surgical-geriatric co-management programme will be implemented in the abdominal surgery department. The aim of this study is to investigate which frailty screening instrument would be best suited to select patients in need of geriatric care and follow-up. If the frailty screening instruments lack discriminatory ability, we will attempt to develop a new prediction model based on collected baseline variables.

## Study objective

Comparative analysis of the diagnostic characteristics of frailty screening instruments to identify a target group that will benefit most from geriatric-surgical co-management to avoid adverse postoperative outcomes, such as postoperative complications (primary outcome), prolonged length of stay (LOS), functional decline, higher level of care needs (secondary outcomes).

# METHODS

## Design and setting

Prospective cohort study in the preoperative outpatient evaluation clinic and the abdominal surgery department of the UH Leuven.

##  Study population

### In- and exclusion criteria

Patients planned for elective colorectal resections for cancer or benign disease in an enhanced recovery after surgery pathway and aged ≥70 years on the day of surgery are eligible for inclusion. Cognitively impaired patients who are still capable of decision making will be included. They can appoint a proxy to assist them in completing the study documents or interviews.

Patients undergoing emergency surgery, reoperations for surgical complications, hyperthermic intraperitoneal chemotherapy, stoma closure or transit repair, rectopexy or prolapse surgery, trans-anal procedures, proctological operations or local stoma procedures will be excluded. Patients whose surgery was omitted or that were not hospitalized in the abdominal surgery department (E 444 / E 445), patients lacking decision making capacity, and patients unable to understand and speak Dutch will also be excluded.

### Sample size and duration

A retrospective study, observing ERAS care in the same study population (S61709), showed that approximately 100 patients per year are eligible for inclusion in the UH Leuven.18 The study duration will be 18 months and assuming 10% refusals, we expect to include a minimum of 135 patients.

Following the guidelines regarding the start of clinical studies after the COVID-19 outbreak, the recruitment will start on 29/06/2020.

## Outcomes

### Primary outcome

* In-hospital Clavien-Dindo ≥ grade 2 postoperative complications.19

### Secondary outcomes

* Prolonged postoperative LOS i.e. LOS ≥ 75th percentile (4 subgroups: open colonic surgery, open rectal surgery, laparoscopic colonic surgery, laparoscopic rectal surgery).
* Functional decline in basic activities of daily living at 1 week and 1, 3, 6 month(s) (defined as the difference in bADL-score compared to the preoperative bADL score)
* Functional decline in instrumental activities of daily living at 1 week and 1, 3, 6 month(s) (defined as the difference in iADL-score compared to the preoperative iADL score)
* Discharge to an increased care level (defined as residence in facility with increased care or increased home-care compared to the preoperative situation)

## Variables

The following variables will be retrieved from the patients’ electronic medical records or obtained by patient interview or questionnaire. Assessment forms are included in **Appendix 1**.

### Variables collected pre-hospital

The **frailty screening instruments** that will be collected pre-hospital are the Fried frailty criteria4 (adjusted version: walking time replaced by Timed-Up-and-Go Test (TUGT)20-22 and Minnesota Leisure Time Activity questionnaire replaced by one question23), Robinson frailty criteria24, Edmonton Frail Scale (EFS)25 (in three versions: the original EFS that includes a TUGT test22 and a Mini-cog test26, the reported Edmonton Frail Scale (rEFS)27, and the modified reported Edmonton Frail Scale (mod-rEFS)28), Rockwood Clinical Frailty Scale29, Modified Frailty Index (in two versions: the 11-item scale (mFI-11)30 and the 5-item scale (mFI-5)31), FRAIL questionnaire32, Geriatric 8 (G8)33 (for original (English) versions and (Dutch) versions used in this study: see **Appendix 2**). The frailty screening instruments are short questionnaires and may also contain short functional tests (**Appendix 1**: B ’preop testen’) and basic laboratory results (**Appendix 1**: D ‘preop dossiernazicht’). In the patient-questionnaire (**Appendix 1**: C ‘Preop assessment’) we divided the questions from the frailty screening instruments into specific themes or ‘geriatric domains’, namely: social situation, health status, selfcare, daily activities, nutritional status, memory, mood, physical performance and falls, vision and hearing, lifestyle habits. The choice of frailty screening instruments that will be compared is this study is based on a best practice guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society and on recommendations for Preoperative Management of Frailty from the Society for Perioperative Assessment and Quality Improvement.7,34 The Geriatric 8 screening tool was added, since it was developed and recommended for older patients with cancer.35,36 About three quarters of the colorectal surgical population in the University Hospitals (UH) Leuven are operated on for cancer.18

In order to describe further baseline characteristics of the included older patient population, the following additional data are collected in the baseline patient questionnaire (**Appendix 1**: C ‘Preop assessment’): Living situation and home care services, the Flemish version of the Triage Risk Screening Tool (fTRST)37), smoking habits and alcohol use, basic activities of daily living (bADL)38, instrumental activities of daily living (iADL)39, vision and hearing problems, Mini Nutritional Assessment (MNA)40, swallowing problems, bladder and bowel function.

The following data will be collected by reviewing the patients’ medical record: Gender, age, height and weight (to calculate the Body Mass Index), preoperative laboratory values (hemoglobin, hematocrit, C-reactive protein, albumin, urea, creatinine,), American Society of Anaesthesiologists (ASA) physical status class41, Charlson Comorbidity Index (CCI)42, Age Adjusted Charlson Comorbidity Index (ACCI)43 (**Appendix 1**: D ‘Preop dossiernazicht’), number and type of medications (**Appendix 1**: E ‘Preop lijst thuismedicatie).

### Variables collected during hospitalisation

Admission date, discharge date, date of surgery, diagnosis, tumour stage and whether or not adjuvant chemo- or radiotherapy in patients with cancer, surgery performed, whether or not a stoma is constructed, type of postoperative complications and their treatment in order to score the overall severity of complications according to the Clavien-Dindo classification (grade 1: no or minor treatment, grade 2: treatment with medication, grade 3: interventional or surgical treatment, grade 4: admission to the intensive care unit)19, number of days in the intensive care unit, mortality, postoperative LOS in days, and discharge destination (**Appendix 1**: D ‘Periop dossiernazicht’).

### Variables collected at 1 week and at 1, 3, 6 month(s) after surgery

The following data will be collected at 1 week and at 1, 3, 6 month(s) after surgery: mortality, place of residence and level of care needs after discharge, bADL38, household activities (according to the EFS25), self-reported acute confusion or cognitive decline since the last contact**.** Thirty-day postoperative complications, 30-day readmission rate, 30-day reoperation rate will be collected 1 month after surgery. (see **Appendix 1**: H ‘Postop 1 week’ / I ‘postop 1 maand’ / J ‘postop 3 maand’ / K ‘postop 6 maand’ assessment’**)**

## Study procedures

### Patient recruitment and informed consent

Patients aged ≥70 years planned for elective colorectal resections will be consecutively recruited during their visit to the preoperative outpatient evaluation clinic (approximately one month before the operation) with an oral and written informed consent by a trained research assistant. Patients that did not attend the preoperative clinic can still be recruited upon admission to the hospital. The recruitment forms are included in **Appendix 1:** A ‘recruitment and end or trial’, and **Appendix 3** (identification form). The informed consent form (ICF) is included in **Appendix 4**.

### Data collection and follow-up

After agreement to participate, three short functional tests will be performed the same day: hand grip strength, mini-cog test, timed-up-and-go test. This will take approximately 5 minutes. The patients will also receive a questionnaire to complete with the research assistant or at home. They will be given the choice between a paper version (with an addressed and stamped envelope) or an electronic version (sent by e-mail if they choose to complete the questionnaire at home). Completion of the questionnaire will take approximately between 10 and 15 minutes.

On admission of the patient to the hospital, the research assistant will collect further study data by consulting the electronic medical record and, if necessary, the treating physician or nurse.

After discharge, patients will be contacted for a telephone interview by the research assistant at 1 week and 1, 3 and 6 month(s) after the operation. The interview will take 5 to 10 minutes. For patients still in hospital the research assistant will collect the data by consulting the electronic medical record and, if necessary, the treating physician or nurse or the patient.

The timeline of the assessments is summarized in **Table 1**. The assessment forms are included in appendices (**Appendix 1 a-k**). In patients declining further participation to the study the date of the last contact and the reason for drop-out will be recorded (**Appendix 3a**).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Time** | **Activity** | **Instrument / type of assessment** | **Content** | **Source** |  | **Assessment by** | **Time to complete** |
| Pre-hospital (outpatient pre-operative consultation clinic) | Informed consent | Informed consent form / oral and written informed consent | Appendix 4 | Patient  |  | Research assistant | 5 min |
| Baseline frailty screening | Functional and cognitive testing: Mini-cog26, TUGT22, Grip strength4 | Appendix 1, part B  | Patient |  | Research assistant | 5 min |
| Questionnaire | Appendix 1, part C | Patient |  | Self-reported questionnaire | 10-15 min |
| Baseline variables | File review | Appendix 1, part D and E | Electronic medical record |  | Research assistant | 10 min |
| During hospitalisation | Baseline and outcome variables | Assessment form  | Appendix 1, part G | Electronic medical record and (if necessary) treating physician/nurse |  | Research assistant | 10 min |
| 1 weekpostop | Follow-up | Questionnaire / telephone interview Assessment form / | Appendix 1, part H  | Patient (if still hospitalised: electronic medical record ± treating physician or nurse) or patient |  | Research assistant | 5-10 min |
| 1 month postop | File review | Appendix 1, part I | Electronic medical record |  | Research assistant | 5 min |
| Questionnaire / telephone interview Assessment form /  | Patient  |  | Research assistant | 5-10 min |
| 3 months postop | File review | Appendix 1, part J | Electronic medical record |  | Research assistant | 5 min |
| Questionnaire / telephone interview Assessment form /  | Patient  |  | Research assistant | 5-10 min |
| 6 months postop | File review | Appendix 1, part K | Electronic medical record |  | Research assistant | 5 min |
| Questionnaire / telephone interview Assessment form /  | Patient  |  | Research assistant | 5-10 min |

**Table 1** Timeline of assessments

##  Data analysis

Descriptive statistics will be used to describe the baseline characteristics and outcomes of our target population. Continuous variables will be reported as means (with standard deviations) for normally distributed data and medians (with interquartile ranges) for non-normally distributed data. Categorical variables will be reported as numbers and percentages.

To compare the performance of the frailty screening instruments, we will examine their predictive value for postoperative outcomes, in particular our primary outcome (the Comprehensive Complication Index) and our secondary outcomes.

Dichotomous outcome variables will be analysed using logistic regression models, and the discriminative value of the screening instruments will be quantified and compared by means of the area under the ROC curve (AUC or C-index). This index takes values between 0.5 and 1, where higher values indicate a higher discriminative value. The diagnostic accuracy of dichotomous frailty screening instruments will further be presented by sensitivity, specificity, negative and positive predictive value.

Continuous outcome variables will be analysed using linear regression models, and the predictive performance of the screening instruments will be quantified and compared by means of the R-square measure. This measure quantifies the proportion of the total variance that is explained by the screening instrument. In case of longitudinally measured outcome variables, linear mixed models will be used, modelling random effects to account for clustering in the data. Such models provide better power compared to separate analyses, and allow to deal with drop-out in a flexible way. The marginal R-square (Nakagawa and Schielzeth (2013)) will then be used to compare predictive performance of the instruments.

If the studied frailty screening instruments show poor performance in outcome prediction in our population, we will attempt to construct a new prediction model, based on baseline characteristics. The akaike information criterion (AIC) will be used to select the best combination of predictor variables. Model performance indicators will be determined as described above, applying internal validation (e.g. k-fold cross validation) to correct for over-optimism.

Statistical analyses will be performed by the Leuven Biostatistics and statistical Bioinformatics Centre L-BioStat.

## Additional data and analyses

We will collect a limited number of additional baseline data, all described above (see 3.3.1.), that will not be included in the primary analyses of this study but that will be used to create a prediction model if the frailty screening instruments lack discriminative ability.

# DATA HANDLING AND DATA MANAGEMENT

Study data will be collected and managed using REDCap®, a secured web application for building and managing electronic surveys and databases. The data will be encoded. Every patient will receive a unique study number and there will be no combination of elements on the data collection forms that allows identification of the individual. Only the project coordinator (JF), the project manager (KF) and the research assistant (LG) will be able to link the data collected in REDCap® to the patients’ electronic medical record using a subject identification log. The document will be stored separately and in a safe location by the project manager (KF) for 10 years, afterwards it will be deleted. The research assistant (LG) will introduce the data in REDCap®. The project manager (KF) will check correct data collection. Data analysis in the framework of this study will be performed by the Leuven Biostatistics and Statistical Bioinformatics Centre. Data collected in this study can be shared with researchers involved in this study upon their request to perform sub analyses. All are affiliated with UZ or KU Leuven. The study does not involve external parties.

# ETHICS

This prospective study will be conducted in compliance with the principles of the Declaration of Helsinki (latest version 2013), the principles of Good Clinical Practice and GDPR and in accordance with all applicable regulatory requirements. The study was approved by the Clinical Trial Centre of the UH Leuven (S-number: S 63864). The Medical Ethics Committee of the UH Leuven is asked for ethical approval. Before the baseline assessment, the research assistant will explain the study to the patients and ask for an oral informed consent. Subsequently, the patients will receive a comprehensive written ICF (**Appendix 4**) and will be given the opportunity to read this form at own pace and to ask questions before signing it. Patients will have the opportunity to read and sign the ICF at home (and return the ICF to the research assistant on admission to the hospital). If a patient appoints a proxy for assistance with completing study documents or interviews, this person will also be asked to sign the ICF. Patients lacking decision-making capacity will be excluded.34 Participation is voluntary and whenever patients wish to discontinue the study they can opt out for any reason, without having to justify their decision. To guarantee the validity of the study, the data collected up to the time of withdrawal will be retained. No new data will be collected. There are no substantial health risks associated with participation in this study: all patients will receive standard care. The measuring of the walking speed carries a small chance of losing balance. However, this test will always be carried out under supervision of a person with a background in healthcare. In the unlikely event that something should go wrong, it is covered by the 'no fault' insurance contract of the UZ / KU Leuven. The patients will not receive any financial compensation for their participation, and will not be charged any costs as a result of any action in this study. There is no funding for this study. Any protocol modification will be sent to the Medical Ethics Committee of the UH Leuven by means of a protocol amendment. There are no conflicts of interest to declare.

# DISSEMINATION AND VALORISATION

## 6.1. Dissemination

The results of the study will be submitted by the core research team as conference abstracts and as publications in professional journals and international peer-reviewed journals. Before the start of the study, a publication policy will be distributed for approval.

## 6.2. Valorisation

This prospective study prepares for the implementation of a surgical-geriatric co-management programme in the abdominal surgery department that is submitted as a Care Strategic Project (UHL call 2020-2024).

# APPENDICES

Appendix 1: Assessment forms (REDCap®)

Appendix 2: Frailty screening instruments

Appendix 3: Recruitment and identification form

Appendix 4: Informed consent form

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