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# BMJ Open

**“The French LARS score”: Validation of the French version of the low anterior resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients**

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3 **“The French LARS score”: Validation of the French version of the low anterior**  
4 **resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-**  
5 **preserving surgery among rectal cancer patients**  
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## Abstract

**Introduction.** Many bowel problems following low anterior resection (LAR) for rectal cancer considerably impair the quality of life (QoL) for patients. The LAR Syndrome (LARS) scale is a self-completion questionnaire to identify and assess bowel dysfunction after rectal cancer surgery. The LARS scale has been translated and validated in several languages but not French (metropolitan French). The primary objective is to adapt the LARS scale to the French language (called French-LARS score) and to assess its psychometric properties. Secondary objectives are, first, to assess both the prevalence and severity of LARS and, second, to measure their impact on QoL.

**Methods and analysis.** A French multicentre observational cohort study was designed and has enrolled 400 patients. The validation study will include translation of the LARS scale following the current international recommendations; assessment of reliability, convergent and discriminant validities, sensitivity, internal consistency, internal validity; and confirmatory analyses. An analysis will be conducted to determine the correlation between the LARS score and the QLQ questionnaires (EORTC's QLQ-C30, QLQ-CR29). Risk factors linked to QoL deterioration will be identified, and their impact will be measured. This study will respond to the need for a validated tool to improve patient care and quality of life.

**Ethics and dissemination.** The institutional review board of the University Hospital of Caen and the ethics committee (CPP Nord Ouest I, January 25, 2019) approved the study. This study is supported by a grant from the French Ministry of Health (PHRC- K17-031). The institutional promoter is the University Hospital of Caen Department of Clinical Research and Innovation (DCRI).

**Trial registration number.** NCT03569488

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3 **Strengths and limitations of this study.**  
4

- 5 - The validation of the French version of the LARS score (the French-LARS score) will allow  
6 the use of a scientific instrument to assess both the prevalence and severity of LARS in  
7 French language.  
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11  
12 - The French-LARS study is a multicentre cohort study of rectal cancer patients  
13 included from 34 units of colorectal surgery in France.  
14  
15  
16  
17 - Limitations include the use of non-probability sampling, which is expected to impose  
18 selection bias.  
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24 **Word count of the manuscript : 3846**  
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28 **Keywords:** bowel dysfunction, rectal cancer, low anterior resection syndrome, colorectal  
29 functional outcome, quality of life, validation  
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## Background

### *Rectal cancer management*

In recent years, progress in the multimodal treatments of rectal cancer (RC) has improved local disease control and increased the survival rate (up to 50% survival at 5 years) [1, 2]. At the same time, the evolution of surgical techniques and the achievement of a 1-cm distal margin below the tumour have pushed back the limits of sphincter-preserving surgery (SPS) without impairing oncological prognosis [3, 4]. In summary, up to 80% of patients with rectal cancer undergo SPS [5]. The assessment of RC outcome has traditionally focused on morbidity rate, tumour recurrence and survival, while functional sequelae (i.e., bowel and/or genitourinary impairment) have long been regarded as inherent to the nature of RC treatments [6, 7]. However, with improved surgical outcomes, we and others have observed a rising number of RC survivors who live with numerous potential side effects and, eventually, an impaired quality of life (QoL) [6-9]. Therefore, bowel function, like QoL, has become an increasingly important focus of care [10].

### *Bowel dysfunction following SPS*

It is widely accepted that as much as 50% to 90% of patients who have an SPS will have a subsequent change in bowel habit [11, 12]. The wide spectrum of bowel symptoms after resection with SPS has been termed the "low anterior resection syndrome (LARS)". The prevalence and severity of LARS remain difficult to assess. Several authors still consider faecal incontinence to be the foremost intestinal sequela, underscoring the impact of urgency and impaired evacuation.

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3 LARS is defined as follows: frequent bowel movements (increased number of stools  
4 during the day and/or night), bowel fractionation (repeated passage of several stools over a  
5 few hours, sometimes requiring the patient to defecate four or five times in 1–2 h); disorders  
6 of continence from minimal gas leaks or staining to debilitating faecal incontinence and  
7 faecal urgency; and urgency (inability to prevent defecation for > 15 min when the need  
8 arises) [11, 12]. These symptoms usually appear immediately after surgery, become most  
9 pronounced during the first few months, improve somewhat thereafter, and reach a steady  
10 state after approximately one to two years [11, 12]. Recently, a pragmatic definition of LARS  
11 has been proposed: "disordered bowel function after rectal resection, leading to a detriment in  
12 QOL" [13].  
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### 29 ***Rationale for the use of the LARS score***

30 Although many questionnaires or instruments have been used to assess the impact of LARS  
31 on QoL, a recent systematic review and meta-analysis observed that 65% of the studies  
32 included did not use a validated assessment instrument [14]. Furthermore, there is  
33 heterogeneity of the assessment tools, namely, single examinations and different scoring  
34 systems, such as the Memorial Sloan Kettering Cancer Center (MSKCC), bowel function  
35 instrument (BFI), Wexner, St. Marks and FSFI scores. The majority of the instruments used  
36 to assess bowel function measured faecal incontinence and omitted other symptoms that have  
37 been shown to have a more significant correlation with quality of life, such as clustering and  
38 urgency [15]. Since 2012, a group of Danish authors have developed and validated a five-  
39 item instrument for the evaluation of LARS (the LARS score – supplementary file) [16]. The  
40 LARS score consists of five items: incontinence for flatus or for liquid stool, frequency of  
41 bowel movements, clustering of stools, and urgency. It allows the categorization of patients  
42 into 3 groups: no LARS (0-20 points), minor LARS (21-29 points), and major LARS (30-42  
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3 points) [16]. It represents the best questionnaire to capture anorectal postoperative function to  
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5 date. When faecal incontinence is the major concern, the Wexner, St. Marks or FSFI score  
6  
7 are adequate; the FSFI is more sound from a methodological viewpoint. While the MSKCC-  
8  
9 FBI is the best questionnaire for the evaluation of LARS, its use is complex. For this reason,  
10  
11 the LARS score is currently used preferentially for first-line evaluation [15]. The ability of  
12  
13 the LARS score to reflect the impact of bowel dysfunction on QOL was proven in its initial  
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15 validation and subsequently through its association with the EORTC QLQ-C30 scale [17]. In  
16  
17 clinical settings, the LARS score severity categories (No LARS, Minor LARS, and Major  
18  
19 LARS) can facilitate quick identification of patients most in need of treatment. Patients with  
20  
21 major LARS reported seriously compromised QOL and significantly worse QOL compared  
22  
23 with those with No/Minor LARS. Consequently, half of the patients restricted their diet and  
24  
25 limited social activity [17].  
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31 In addition to the original Danish version, the LARS score has been translated into  
32  
33 several other languages (English, Dutch, Swedish, Spanish, German, and Chinese) and has  
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35 the capacity for widespread use [18-20].  
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### 40 ***Hypothesis and objectives of the investigations***

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42 Both the adoption of a uniform definition of LARS and the consistent use of the same  
43  
44 questionnaire allow researchers to pool and compare the results of different studies and  
45  
46 institutions. A validated French version of the LARS score is not yet available.  
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49 The main objective will be to adapt and validate the LARS scale questionnaire to the French  
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51 language (called French-LARS score) and assess its psychometric properties. Secondary  
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53 objectives are, first, to assess both the prevalence and severity of LARS and, second, to  
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55 measure their impact on QoL.  
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## Methods

### *Study design*

The French-LARS study is an observational, multicentre, cohort study of rectal cancer patients who underwent curative sphincter-preserving surgery with partial or total mesorectal excision.

Patients are included from 34 units of colorectal surgery in France (see list of participating centres in the Acknowledgements section). The study has been approved by the scientific board of the French Research Group of Rectal Cancer Surgery (GRECCAR) group. This group was created by surgical teams in France who are involved in the management of rectal cancer with the aim of conducting and publishing multicentre clinical trials on the subject in high-level journals and expanding this surgical specialty to various learned societies. Most of the participating teams in the study are affiliated with the GRECCAR group. All investigators will proceed with this study in accordance with the Declaration of Helsinki.

### *Study population*

All patients provided written informed consent prior to their enrolment for study participation.

The patient inclusion and exclusion criteria are as follows:

#### Inclusion criteria

- Patients aged between 18 and 80 years
- Rectal cancer patients who underwent curative sphincter-preserving surgery with partial or total mesorectal excision
- Surgery performed between January 2007 and January 2017, with reversal of the defunctioning stoma before January 2017

- Bowel continuity restored for at least 24 months.
- Voluntary participation in the study

#### Exclusion criteria

- A palliative rectal cancer resection
- The presence of stoma
- Known disseminated or recurrent disease
- Cognition and/or language issues.

For patients lost to follow-up, an active search will be carried out with the general practitioners and, if necessary, with the birth councils in order to know the vital status.

Participants in the validation study will be identified through local databases by the investigators at each of the participating centres. They will be selected randomly from the pool of eligible subjects. Participants will be approached following a minimum duration of 24 months after surgery to allow their bowel function to have regained stability [11, 12, 17].

#### ***Data collected***

Demographic and clinical information will be obtained from the databases. Patient characteristics will be collected on e-CRFs (electronic Case Report Forms) and include age, sex, body mass index, tumour height (distance from anal verge on MRI or rigid sigmoidoscopy in centimetres), timing and type of neoadjuvant radiotherapy and chemotherapy if it was recommended; time since surgery; type of surgery (PME or TME); type of anastomosis; defunctioning stoma; and postoperative mortality and morbidity such as pelvic abscess, anastomotic leakage, and reoperation. Morbidity will be evaluated with the new classification of surgical complications by Dindo et al. [21], which includes 5 grades. The usual data will be recorded: distal and circumferential margins, the number of resected and invaded nodes, tumoural differentiation, the presence of vascular embols (venous or

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3 lymphatic, intra- or extra-mural), perineural enhancement, and the quality of the mesorectal  
4 excision. The resected specimen will be staged according to American Joint Committee on  
5 Cancer (AJCC) criteria (7th version).  
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10 Data collection will be performed according to the following procedures. (i) The  
11 researchers will identify eligible participants by reviewing the medical records of rectal  
12 cancer patients. (ii) The eligible patients will be contacted by postal invitation and will be  
13 informed about the purpose of the study. (iii) The completed questionnaires will be carefully  
14 checked by the researchers for any missing information. The eligible patients will be  
15 contacted by postal invitation twice for lack of response. Any unclear item of missing  
16 information will be reconfirmed through a phone call. If this is not possible, the questionnaire  
17 will be considered invalid.  
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### 31 ***Study end points***

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33 The primary objective is to validate a French-language version of the LARS score: to adapt  
34 the LARS scale questionnaire to the French language (called French-LARS score) and to  
35 assess its psychometric properties and factor structure.  
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40 The secondary objectives are, first, to assess both the prevalence and severity of  
41 LARS and, second, to measure their impact on QoL.  
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### 47 ***Detailed description of the implemented techniques***

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49 The validation study of the French version of the LARS score is based on face and content  
50 validities as well as on the measurement of its psychometric properties in compliance with  
51 the standards published by the American Educational Research Association et al. [22].  
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### 58 ***Validation study of the French version***

### ***Translation process***

After obtaining permission from the original authors [18, 19], we will conduct the forward- and back-translation procedures in accordance with the translation guidelines provided by the authors.

The French-LARS questionnaire will be developed by translating the questions into French, a task that will be performed by two independent translators who are native French speakers with a high level of fluency. The two translators will check and discuss the two translations only for inconsistency and will establish a single preliminary French version. Thereafter, the French version will be back-translated into English by two independent professional translators; both are fluent in French and with English as their mother tongue, and both are unfamiliar with the background objectives of the study. Both versions of the backward translation will be compared with each other and with the initial version; after minor adjustments, a final French version will be agreed upon. The final French version and the whole translation process mentioned above will be sent to the original authors for approval.

### ***Content validity***

Assessment of content validity will be carried out by a panel of experts during the process that will lead to the final French version of the scale. Each expert will independently judge, by means of a Likert scale with 3 possible answers (poor, average and good), whether the content from the original LARS-score is preserved and adapted in the French language (see Acknowledgement).

### ***Face validity and perceived validity***

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3 Then, a pilot study will be conducted. The French questionnaire (called French-LARS score)  
4 will be administered to 100 patients in order to verify the adequacy and degree of  
5  
6 comprehension of the questions (figure1). These patients will be chosen according to their  
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8 representativeness (i.e., a wide range of socio-demographic and clinical characteristics). In  
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10 total, male patients and female patients will be administered the questionnaire. These patients  
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12 with have primary education levels, secondary education levels, and college or higher  
13  
14 education levels. Patients will have tumour stages I, II and III.  
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19 Each patient using the French-LARS score will be asked to review the questionnaire  
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21 by precisely pointing out all of the difficulties encountered when using the instrument,  
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23 including:  
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- 26 • items that are ambiguous or badly formulated
- 27
- 28 • difficulties or confusion completing the scale
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30 Each patient will be asked to indicate whether the questionnaire is acceptable and  
31  
32 easy to understand.  
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### 38 ***Reliability***

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40 Reproducibility will be investigated by a test-retest procedure. A randomly selected subgroup  
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42 of participants (n= 400) will be sent the French-LARS score questionnaire twice (figure1).  
43  
44 The second test will be sent to the participants one or two weeks after the completion of the  
45  
46 first test. Patients will be asked if they have experienced any significant change in bowel  
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48 function between the first and the second test. Those confirming a change in bowel function  
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50 will be excluded from the test-retest analysis. Non-responders will be further contacted twice,  
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52 either via postal invitation or by phone. The test-retest study will be performed by comparing  
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54 the French-LARS scores obtained at the two time points. The test-retest reliability of the  
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56 questionnaire will be assessed by Cohen's Kappa coefficient (no LARS, minor LARS and  
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3 major LARS scores) or by intra-class correlation coefficient, ICC (quantitative LARS score).

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5 Internal consistency will be estimated by the Cronbach alpha coefficient.

### 6 7 8 ***Convergent validity***

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10 The convergent validity will notably be determined in this study by computing the  
11 correlations between the French-LARS score and the EORTC QLQ-C30 and QLQ-CR29  
12 domains [23], which have been globally accepted and widely used as valid instruments for  
13 measuring QoL. Thus, eligible patients will receive a postal invitation to complete the  
14 EORTC QLQ-C30 and QLQ-CR29 along with the French-LARS scores. Furthermore, to  
15 study the convergent validity between qualitative measures of the LARS scores (no LARS,  
16 minor LARS and major LARS) and quality of life, the patients will be asked a general  
17 question [16, 19]: “Overall, how much does your bowel function affect your quality of life?”  
18 Four mutually exclusive responses, “not at all”, “very little”, “somewhat” or “a lot”, will be  
19 proposed.  
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### 35 36 ***Discriminant validity***

37 With regard to the scoring instructions for these two instruments, a high score represents a  
38 high QoL or a high level of functioning for the global QoL subscale and functional subscale.  
39 However, for a symptom subscale/item, the higher the score, the more severe the symptom.  
40 The ability to discriminate between patients with different clinical characteristics is necessary  
41 for an instrument to be considered valid. For discriminant validity testing, we will use known  
42 variables, including gender, age, neoadjuvant radiation therapy, distance of the tumour from  
43 the anal verge, prior temporary stoma, length of postoperative period (time since stoma-free  
44 rectal resection surgery or reversal surgery from temporary stoma) and postoperative septic  
45 complications such as pelvic abscess or anastomotic leakage. These variables are known to  
46 affect bowel function after SPS in rectal cancer patients [11-13, 24]. The following numeric  
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3 variables will be changed into binary variables: age, distance of the tumour from the anal  
4 verge, and length of the postoperative period; the median value for each will serve as the  
5  
6 cutoff point. Radiotherapy and prior temporary stoma will be treated as dichotomous  
7  
8 variables: no treatment at all versus treatment. The EORTC will provide us with and  
9  
10 authorize our use of the French version of the two questionnaires.  
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### 17 ***Sensitivity of the items***

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19 A search for the ceiling or floor effects will be systematically be made.  
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### 23 ***Internal consistency***

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25 Internal consistency will be assessed using Cronbach's alpha coefficient.  
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### 30 ***Internal validity***

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32 A factorial analysis will allow verification of the internal structure of the scale. The statistical  
33  
34 method used is described below.  
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### 40 ***Confirmatory analysis***

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42 A confirmatory analysis will be conducted to evaluate the recognized structural validity of  
43  
44 the scale in regard to its first edition.  
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### 49 ***Statistical analysis***

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51 Quantitative variables will be expressed as the mean  $\pm$  standard deviation (SD), and  
52  
53 qualitative variables will be expressed as the number of patients and percentages.  
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56 The experimental design of the study leads to the same patient being seen several  
57  
58 times during his oncology follow-up. However, apart from the subgroup of patients who  
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3 participate in the study of repeatability, each patient will complete only one questionnaire in  
4  
5 the study.  
6

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8 The comparisons between the mean scores of the three groups (no LARS, minor  
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10 LARS or major LARS) will be carried out with the help of an analysis of variance or a  
11  
12 Kruskal-Wallis test depending on whether the data follow the verified homoscedasticity  
13  
14 hypothesis or not. The post hoc comparisons will rely on the Bonferroni correction or the  
15  
16 Nemenyi test.  
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18  
19 The factor analysis will rely on a principal component analysis. The selected factors  
20  
21 will correspond to an eigenvalue  $\geq 1$ .  
22

23  
24 The repeatability test (test-retest), in which 400 patients will be asked to complete the  
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26 F-LARSF-LARSF-LARS twice within 15 days will use the student's *t*-test for repeated  
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28 measurements and, with the help of the intraclass correlation coefficient (ICC) and its 95%  
29  
30 CI, will use the ANOVA for random effects models. After estimating the various components  
31  
32 of the total variance, the ICC will be calculated in the usual manner. A graphic representation  
33  
34 from Bland and Altman will show the level of agreement of the repeatability test.  
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37  
38 The sensitivity and specificity of the French-LARS score in predicting the impact on  
39  
40 quality of life (QoL) will be assessed by receiver operating characteristic (ROC) curves of the  
41  
42 score versus groups reporting no/minor or some/major impact on QoL.  
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44  
45 The correlation between the LARS validated score and the QLQ questionnaires  
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47 (EORTC's QLQ-C30, QLQ-CR29) will be estimated with the Pearson correlation coefficient  
48  
49 as well as with the Spearman correlation coefficient and its 95% confidence interval.  
50

51  
52 The inclusion of the data indicating the impact of LARS on quality of life will be  
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54 based on a univariate approach and then a multivariate approach using ad hoc models  
55  
56 following the nature of the dependent variable (binary or multinomial logistic regression or  
57  
58 linear regression depending on whether the quality of life score is considered qualitative or  
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3 quantitative). Only variables whose level of significance in the univariate analysis is  $p < 0.15$   
4  
5 will be included in the multivariate model. This approach will enable the individualization of  
6  
7 the risk factors linked to a deterioration of the quality of life and an evaluation their impact.  
8  
9

10 The confirmatory analysis will rely on structural equation models that enable the  
11  
12 validation of the measurement structure of various concepts.  
13

14 All of the tests will be two-sided with a level of significance ( $p$ ) that equals 0.05.  
15  
16 IBM®-SPSS® 22.0 and AMOS for Windows® software will allow the calculations.  
17  
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### 21 ***Feasibility***

22  
23 Thirty-four colorectal cancer centres, including both university hospitals and cancer control  
24  
25 centres, gave their consent to include between 50 and 100 patients who had undergone SPS  
26  
27 from 2007 to 2017 (see the list of participating centres in the Acknowledgements section).  
28  
29 The availability of patients for study inclusion from each GRECCAR's team has been  
30  
31 demonstrated in published randomized studies [25-28]). We chose to include patients who  
32  
33 underwent SPS between 2007 and 2017 for two reasons. First, the French recommendations  
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35 for clinical practice and therapeutic choices for rectal cancer were published after 2007,  
36  
37 which make the diagnoses and therapeutic strategies homogeneous [10]. Second, participants  
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39 were approached a minimum of 24 months after surgery to allow their bowel function to have  
40  
41 regained stability [11, 18, 19]. Finally, eligible participants are usually monitored in each  
42  
43 centre at regular intervals to screen for local recurrence and/or distant metastasis. For all of  
44  
45 these reasons, approximately 3000 patients will be contacted in order to include more than  
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47 1000 patients, expecting a 33% response rate.  
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### 56 ***Registration***

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3 The data will be collected and registered in e-CRFs by a dedicated local technical research  
4 team using the Ennov Clinical software.  
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### 10 ***Study organization***

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12 Promotion of this study will be performed by the University Hospital of Caen, France. The  
13 study is funded, thanks to the financial support received from the Program for Hospital  
14 Clinical Cancer Research “**INCa-DGOS\_12112**”.  
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### 21 ***Duration and timeline***

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23 Patients will be included during 12 months. The protocol approval from the ethical  
24 committee, financial support, and e-CRFs were developed in 2018 and 2019. Recruitment of  
25 the patients is planned to continue until the first semester of 2021. The database will be  
26 closed in 2021, after which data analysis, manuscript writing, and submission for publication  
27 will follow (figure 2).  
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### 38 ***Ethics***

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40 The institutional review board of the University Hospital of Caen and the ethics committee  
41 (CPP Nord Ouest I, January 25, 2019) approved the study. The French-LARS study was  
42 registered on January 28, 2019, on the ClinicalTrials.gov Web site with trial identification  
43 number NCT03569488. This study is supported by a grant from the French Ministry of  
44 Health (PHRC- K17-031). The institutional promoter is the University Hospital of Caen  
45 Department of Clinical Research and Innovation (DCRI).  
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### 56 **Discussion**

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3 Although the prevalence and severity of LARS remain difficult to assess, the LARS score,  
4 which has been developed and validated for seven years, represents the best questionnaire to  
5 capture anorectal postoperative function to date [15]. However, a validated French version of  
6 the LARS score is not yet available. This instrument (the French-LARS score) will allow for  
7 the development of future research and clinical practice in France. LARS remains a major  
8 problem, but it is not well understood among healthcare professionals, and it is frequently  
9 underestimated. Furthermore, there is considerable discrepancy between the clinician's  
10 judgement of patient perception and the patient's actual view or experience [25, 26]. For  
11 example, specialists tend to overestimate the impact of incontinence and frequent bowel  
12 movements, while they underestimate the impact of urgency and clustering [25]. Therefore,  
13 knowledge of therapeutic options such as transanal irrigation, biofeedback, or sacral nerve  
14 stimulation for patients with LARS is limited [27-29]. These recent studies have indicated  
15 that there is a need for improved LARS education for clinicians [25, 26]. There is now  
16 evidence that both the distribution of patients within different LARS groups (minor and/or  
17 major) and the impact of LARS on QoL did not change over time [30]. According to recent  
18 studies [31], nearly 50% of patients still experienced major LARS 13 to 15 years after  
19 surgery. Interestingly, only major LARS has an impact on the patients' QoL [32].

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21  
22 A 2019 survey highlights the notable functional consequences reported by RC  
23 survivors after SPS surgery [33]. Based on validated instruments, 40% of RC survivors  
24 suffered from a major LARS episode that significantly impaired their quality of life. More  
25 interestingly, bowel dysfunction was the only predictor of QoL for such patients after  
26 adjustment for age and different QoL components (urinary and sexual function) [33].

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29 The validation of the French LARS score will allow us to use a scientific instrument  
30 that might be used in daily clinical practice not only to identify patients with elevated LARS  
31 scores but also to predict bowel dysfunction for prevention and rapid management. It will  
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3 hopefully lead to improve clinician awareness in order to improve both the prevention and  
4 treatment of bowel dysfunction and the information given to patients. In the future, we will  
5 be able to develop a new patient-led follow-up programme based on symptom burden and  
6 health-related QoL.  
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12 In this way, a recently published nomogram “the POLARS score” was developed to  
13 predict bowel dysfunction severity prior to anterior resection [34]. Theoretically, this tool  
14 allows clinicians to personalize care during multidisciplinary team meetings, to prepare  
15 patients for the consequences of treatment, and to guide the treatment decision with patient  
16 consent.  
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23 Another alternative strategy for high-risk patients called the “watch-and-wait” policy  
24 has been proposed in cases of complete clinical response following chemo-radiation therapy.  
25 Although this strategy provides fewer functional problems than rectal resection, major LARS  
26 symptoms have been reported in up to one-third of these patients [35]. However, there is, to  
27 date, insufficient evidence to draw firm conclusions on the oncological safety of this  
28 approach.  
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37 In summary, the validation of the French version of the LARS score (the French-  
38 LARS score) will allow the use of a scientific instrument to assess both the prevalence and  
39 severity of LARS.  
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44 Together with the oncological data, it will be important to discuss functional  
45 outcomes with patients as well.  
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**List of abbreviations**

C30 : Core 30

CR 29 : Colo Rectal 29

CRF : Case Report Form

DCRI : Department of Clinical Research and Innovation

eCRF : electronic Case Report Form

EORTC : European Organization for Treatment and Research of Cancer

FSFI : Female Sexual Function Index

ICC : Intraclass Correlation Coefficient

QLQ : Quality of Life Questionnaire

LARS : Low Anterior Resection Syndrom

MSKCC : Memorial Sloan Kettering Cancer Center

PME : Partial Mesorectal Excision

POLARS : Pre-Operative Low Anterior Resection Syndrom

QoL : quality of life

RC : Rectal Cancer

SD : Standard Deviation

SPS : Sphincter-preserving surgery

TME : Total Mesorectal Excision

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9  
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13

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15  
16 Study conception and design: AA, VB, RM, YE. Intervention design: RM, AA, VB, YE,  
17  
18 JJD, FC, YC, JJD, BM and YE. Analysis of data will be done by YE, OD and RM.  
19  
20  
21 AA drafted the work and was revised critically for intellectual content by TJ. All authors  
22  
23 gave final approval of this version to be published.  
24  
25

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27  
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29  
30 Clinical Cancer Research “INCa-DGOS\_12112”.  
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### 33 ***Competing interests***

34  
35 None declared.  
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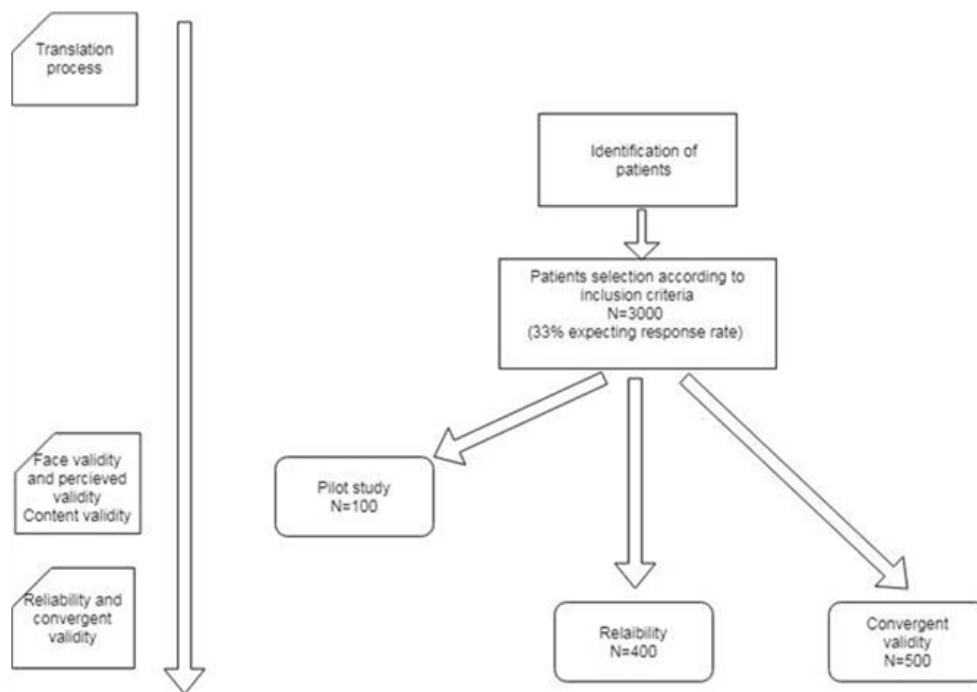


Figure 1 -Consort Diagram: Flow of the participants throughout the study

144x100mm (120 x 120 DPI)

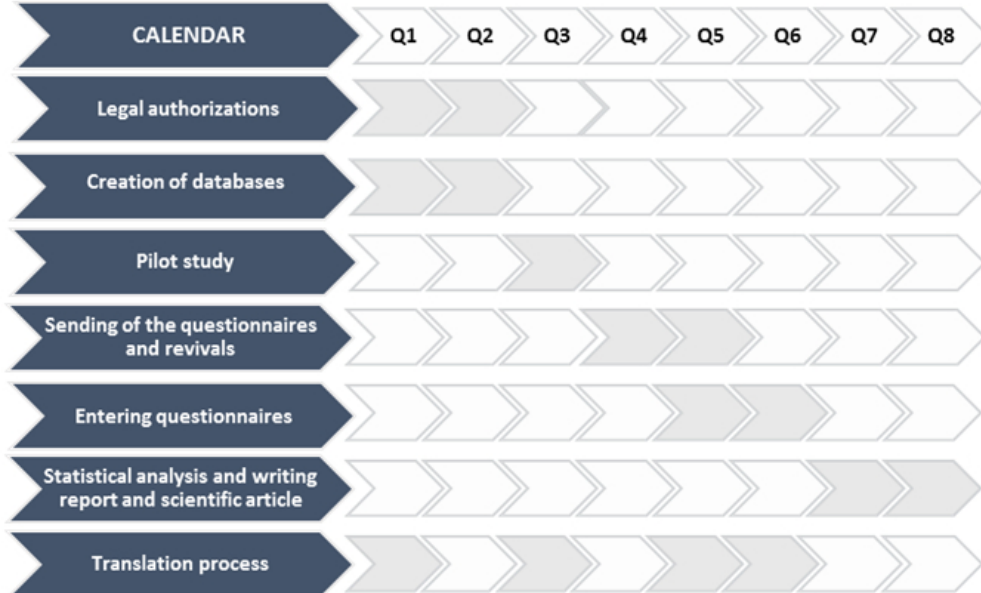


Figure 2 - Forecasting steps adapted to the study

142x86mm (120 x 120 DPI)

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## The LARS Score - Scoring Instructions

Add the scores from each 5 questions to one final score.

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### Do you ever have occasions when you cannot control your flatus (wind)?

- |   |          |
|---|----------|
| <input type="checkbox"/> No, never                    | <b>0</b> |
| <input type="checkbox"/> Yes, less than once per week | <b>4</b> |
| <input type="checkbox"/> Yes, at least once per week  | <b>7</b> |

### Do you ever have any accidental leakage of liquid stool?

- |   |          |
|---|----------|
| <input type="checkbox"/> No, never                    | <b>0</b> |
| <input type="checkbox"/> Yes, less than once per week | <b>3</b> |
| <input type="checkbox"/> Yes, at least once per week  | <b>3</b> |

### How often do you open your bowels?

- |   |          |
|---|----------|
| <input type="checkbox"/> More than 7 times per day (24 hours) | <b>4</b> |
| <input type="checkbox"/> 4-7 times per day (24 hours)         | <b>2</b> |
| <input type="checkbox"/> 1-3 times per day (24 hours)         | <b>0</b> |
| <input type="checkbox"/> Less than once per day (24 hours)    | <b>5</b> |

### Do you ever have to open your bowels again within one hour of the last bowel opening?

- |   |           |
|---|-----------|
| <input type="checkbox"/> No, never                    | <b>0</b>  |
| <input type="checkbox"/> Yes, less than once per week | <b>9</b>  |
| <input type="checkbox"/> Yes, at least once per week  | <b>11</b> |

### Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

- |   |           |
|---|-----------|
| <input type="checkbox"/> No, never                    | <b>0</b>  |
| <input type="checkbox"/> Yes, less than once per week | <b>11</b> |
| <input type="checkbox"/> Yes, at least once per week  | <b>16</b> |

**Total Score:**

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### Interpretation:

- 0-20: No LARS**  
**21-29: Minor LARS**  
**30-42: Major LARS**



# BMJ Open

## **“The French LARS score”: Validation of the French version of the low anterior resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients: a study protocol**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034251.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Dec-2019
Complete List of Authors:	Eid, Yassine; Centre Hospitalier Universitaire de Caen, digestive surgery; UMRS 1086, Bouvier, Véronique; Cancers et préventions Dejardin , Olivier; Cancers et préventions Menahem, Benjamin; Centre Hospitalier Universitaire de Caen Chaillot, Fabien; Centre Hospitalier Universitaire de Caen Chene, Yannick; Centre Hospitalier Universitaire de Caen Dutheil, Jean Jacques; Centre Hospitalier Universitaire de Caen Juil, Therese; Aarhus Univ Hosp Morello, Rémy; Centre Hospitalier Universitaire de Caen Alves, Arnaud; Centre Hospitalier Universitaire de Caen
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery
Keywords:	bowel dysfunction, rectal cancer, low anterior resection syndrome, colorectal functional outcome, quality of life, validation

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3 **“The French LARS score”**: Validation of the French version of the low anterior  
4 **resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-**  
5 **preserving surgery among rectal cancer patients: a study protocol**  
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## Abstract

**Introduction.** Many bowel problems following low anterior resection (LAR) for rectal cancer considerably impair the quality of life (QoL) of patients. The LAR Syndrome (LARS) scale is a self-report questionnaire to identify and assess bowel dysfunction after rectal cancer surgery. It has been translated and validated in several languages but not in French (metropolitan French). The primary objective is to adapt the LARS scale to the French language (called French-LARS score) and to assess its psychometric properties. Secondary objectives are to assess both the prevalence and severity of LARS and to measure their impact on QoL.

**Method and analysis.** A French multicentre observational cohort study has been designed. The validation study will include translation of the LARS scale following the current international recommendations, assessment of its reliability, convergent and discriminant validities, sensitivity, internal consistency, internal validity, and confirmatory analyses. One thousand patients will be enrolled for the analyses. The questionnaire will be initially administered to the first 100 patients in order to verify the adequacy and degree of comprehension of the questions. Then reproducibility will be investigated by a test-retest procedure in the following 400 patients.

An analysis will be conducted to determine the correlation between the LARS score and the QLQ questionnaires (EORTC's QLQ-C30, QLQ-CR29). Risk factors linked to QoL deterioration will be identified and their impact will be measured. This study will meet the need for a validated tool to improve patient care and QoL.

**Ethics and dissemination.** The institutional review board of the University Hospital of Caen and the ethics committee (CPP Nord Ouest I, January 25, 2019) approved the study. This study is supported by a grant from the French Ministry of Health (PHRC- K17-031). The

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3 institutional promoter is the University Hospital of Caen Department of Clinical Research  
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5 and Innovation (DCRI).  
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8 **Trial registration number.** NCT03569488  
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10 **Strengths and limitations of this study.**  
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12 - The validation of the French version of the LARS score (the French-LARS score) will allow  
13 the use of a scientific instrument to assess both the prevalence and severity of LARS in  
14 French language.  
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17 - The French-LARS study is a multicentre cohort study of rectal cancer patients  
18 included from 34 units of colorectal surgery in France.  
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21 - Limitations include the use of non-probability sampling, which is expected to impose  
22 selection bias.  
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24 **Word count of the manuscript : 4302 words**  
25

26 **Keywords:** bowel dysfunction, rectal cancer, low anterior resection syndrome, colorectal  
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28 functional outcome, quality of life, validation  
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## Manuscript

### Background

#### *Rectal cancer management*

In recent years, progress in the multimodal treatments of rectal cancer (RC) has improved local disease control and increased the survival rate (up to 50% survival at 5 years) [1, 2]. At the same time, the evolution of surgical techniques and the achievement of a 1-cm distal margin below the tumour have pushed back the limits of sphincter-preserving surgery (SPS) without impairing oncological prognosis [3, 4]. Up to 80% of patients with RC undergo SPS [5]. The assessment of RC outcome has traditionally focused on morbidity rate, tumour recurrence and survival, while functional sequelae (i.e., bowel and/or genitourinary impairment) have long been regarded as inherent to the nature of RC treatments [6, 7]. However, with improved surgical outcomes, we and others have observed a rising number of RC survivors who live with numerous potential side-effects and, eventually, an impaired quality of life (QoL) [6-9]. Therefore, bowel function, like QoL, has become an increasingly important focus of care [10].

#### *Bowel dysfunction following SPS*

It is widely accepted that as many as 50% to 90% of patients who undergo SPS will have a subsequent change in bowel habit [11, 12]. The wide spectrum of bowel symptoms after resection with SPS has been termed the "low anterior resection syndrome (LARS)". The prevalence and severity of LARS remain difficult to assess. Several authors still consider faecal incontinence to be the foremost intestinal sequela, underscoring the impact of urgency and impaired evacuation.

LARS is defined as follows: frequent bowel movements (increased number of stools during the day and/or night); clustering (repeated passage of several stools over a few hours, sometimes requiring the patient to defecate four or five times in 1–2 h); disorders of

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3 continence from minimal gas leaks or staining to debilitating faecal incontinence and faecal  
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5 urgency; and urgency (inability to prevent defecation for > 15 min when the need arises) [11,  
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7 12]. These symptoms usually appear immediately after surgery, become most pronounced  
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9 during the first few months, improve somewhat thereafter, and reach a steady state after  
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11 approximately one to two years [11, 12]. Recently, a pragmatic definition of LARS has been  
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13 proposed: "disordered bowel function after rectal resection, leading to a detriment in QOL"  
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15 [13].  
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### 22 ***Rationale for using the LARS score***

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24 Although many questionnaires or instruments have been used to assess the impact of LARS  
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26 on QoL, a recent systematic review and meta-analysis observed that 65% of the studies  
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28 included did not use a validated assessment instrument [14]. Furthermore, there is a wide  
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30 range of assessment tools, including single examinations and different scoring systems, such  
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32 as the Memorial Sloan Kettering Cancer Center (MSKCC) score, the bowel function  
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34 instrument (BFI), and the Wexner, St. Marks and FSFI scores. Most of the instruments used  
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36 to assess bowel function measure faecal incontinence but leave aside other symptoms that  
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38 have been shown to have a more significant correlation with QoL, such as clustering and  
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40 urgency [15]. Since 2012, a group of Danish authors has developed and validated a 5-item  
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42 instrument for the evaluation of LARS: the LARS score [16]. The items are incontinence for  
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44 flatus or for liquid stool, frequency of bowel movements, clustering of stools, and urgency. It  
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46 allows the categorization of patients into three groups: no LARS (0-20 points), minor LARS  
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48 (21-29 points), and major LARS (30-42 points) [16]. To date, it is the best questionnaire for  
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50 capturing anorectal postoperative function. When faecal incontinence is the major concern,  
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52 the Wexner, St. Marks or FSFI scores are adequate, the latter being the most sound from a  
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54 methodological viewpoint. While the MSKCC-FBI is the best questionnaire for evaluating  
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3 LARS, its use is complex. For this reason, the LARS score is currently used preferentially for  
4 first-line evaluation [15]. Its ability to reflect the impact of bowel dysfunction on QoL was  
5 proven in its initial validation and subsequently through its association with the EORTC  
6 QLQ-C30 scale [17]. In clinical settings, its severity categories (No LARS, Minor LARS, and  
7 Major LARS) can facilitate rapid identification of patients most in need of treatment. Patients  
8 with major LARS reported seriously compromised QoL and significantly worse QoL  
9 compared with those with No/Minor LARS. Consequently, half of the patients restricted their  
10 diet and limited their social activity [17]. In addition to the original Danish version, the  
11 LARS score has been translated into English, Dutch, Swedish, Spanish, German and Chinese,  
12 and can potentially be used widely[18-20].  
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### 29 *Hypothesis and objectives of the investigations*

30 Both the adoption of a uniform definition of LARS and the consistent use of the same  
31 questionnaire allow researchers to pool and compare the results of different studies and  
32 institutions. . However, a validated French version of the LARS score is not yet available.  
33 The main objective therefore will be to adapt and validate the LARS scale questionnaire to  
34 the French language (called French-LARS score) and assess its psychometric properties.  
35 Secondary objectives are to assess both the prevalence and severity of LARS and to measure  
36 their impact on QoL.  
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### 49 **Methods**

#### 50 51 52 53 *Study design*

54 The French-LARS study is an observational, multicentre, cohort study of rectal cancer  
55 patients who have undergone curative sphincter-preserving surgery with partial or total  
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mesorectal excision. Patients are included from 34 units of colorectal surgery in France (see list of participating centres in the Acknowledgements section). The study has been approved by the scientific board of the French Research Group of Rectal Cancer Surgery (GRECCAR). This group was created by surgical teams in France who are involved in the management of rectal cancer, with the aim of conducting and publishing multicentre clinical trials on the subject in high-level journals and expanding this surgical specialty to various learned societies. Most of the participating teams in the study are affiliated with the GRECCAR. All investigators will proceed with this study in accordance with the Declaration of Helsinki.

### ***Study population***

All patients will provide written informed consent prior to their enrolment for study participation.

The inclusion criteria are as follows: aged between 18 and 80 years; rectal cancer patients who have undergone curative sphincter-preserving surgery with partial or total mesorectal excision; surgery performed between January 2007 and January 2017, with reversal of the defunctioning stoma before January 2017; bowel continuity restored for at least 24 months (including the reversal of the temporary stoma); voluntary participation in the study. The exclusion criteria are as follows: a palliative rectal cancer resection; presence of stoma; known disseminated or recurrent disease; cognition and/or language issues.

For patients lost to follow-up, an active search will be carried out with general practitioners and, if necessary, with the birth councils in order to know the vital status. Participants in the validation study will be identified through local databases by the investigators at each of the participating centres. They will be selected randomly from the pool of eligible subjects.

Participants will be approached not earlier than 24 months after surgery to allow their bowel function to have regained stability [11, 12, 17].

### ***Data collected***

Demographic and clinical information will be obtained from the databases. Patient characteristics will be collected on e-CRFs (electronic Case Report Forms) and include age, sex, body mass index, tumour height (distance from anal verge on MRI or rigid sigmoidoscopy in centimetres), timing and type of neoadjuvant radiotherapy and chemotherapy, if recommended; time since surgery; type of surgery (PME or TME); type of anastomosis; defunctioning stoma; and postoperative mortality and morbidity such as pelvic abscess, anastomotic leakage, and reoperation. Morbidity will be evaluated with the new classification of surgical complications by Dindo et al. [21], which includes five grades. The usual data will be recorded: distal and circumferential margins, the number of resected and invaded nodes, tumoral differentiation, the presence of vascular emboli (venous or lymphatic, intra- or extra-mural), perineural invasion, and the quality of the mesorectal excision. The resected specimen will be staged according to American Joint Committee on Cancer (AJCC) criteria (7th version).

Data collection will be performed according to the following procedures. (i) The researchers will identify eligible participants by reviewing the medical records of rectal cancer patients. (ii) Eligible patients will be contacted by postal invitation and will be informed about the purpose of the study. (iii) The completed questionnaires will be carefully checked by the researchers for any missing information. Eligible patients will be contacted by postal invitation twice if they do not reply. Any unclear item of missing information will be reconfirmed through a phone call. If this is not possible, the questionnaire will be considered invalid.

### ***Study endpoints***

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3 The primary objective is to validate a French-language version of the LARS score, to adapt  
4 the LARS scale questionnaire to the French language (called French-LARS score) and to  
5 assess its psychometric properties and factor structure. The secondary objectives are to assess  
6 both the prevalence and severity of LARS and to measure their impact on QoL.  
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### 14 ***Detailed description of implemented techniques***

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17 The validation study of the French version of the LARS score is based on face and content  
18 validity as well as on the measurement of its psychometric properties, in compliance with the  
19 standards published by the American Educational Research Association et al. [22].  
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### 26 ***Validation study of French version***

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28 The different steps are detailed in figure 1 and figure 2.  
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### 30 ***Translation process***

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33 After obtaining permission from the original authors [18, 19], we will conduct the forward-  
34 and back-translation procedures in accordance with the translation guidelines provided by the  
35 authors. The French-LARS questionnaire will be developed by translating the questions into  
36 French, a task that will be performed by two independent translators who are native French  
37 speakers with a high level of fluency. The two translators will check and discuss the two  
38 translations only for inconsistency and will establish a single preliminary French version.  
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40 Thereafter, the French version will be back-translated into English by two independent  
41 professional translators; both are fluent in French and with English as their mother tongue,  
42 and both are unfamiliar with the background objectives of the study. Both versions of the  
43 backward translation will be compared with each other and with the initial version. After  
44 minor adjustments, a final French version will be agreed upon. The final French version and  
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3 the whole translation process mentioned above will be sent to the original authors for  
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5 approval.  
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### 10 ***Content validity***

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12 Content validity will be assessed by a panel of experts during the process, which will lead to  
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14 the final French version of the scale. Using a 3-point Likert scale (poor, average and good),  
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16 each expert will judge independently whether the content from the original LARS score is  
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18 conserved and adapted in the French language (see Acknowledgements).  
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### 23 ***Face validity and perceived validity***

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25 Then, a pilot study will be conducted. The French LARS score will be administered to 100  
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27 patients in order to verify the adequacy and degree of comprehension of the questions (figure  
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29 1). These patients will be chosen according to their representativeness based on a wide range  
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31 of socio-demographic and clinical characteristics. Both male and female patients will  
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33 complete the questionnaire. They will have primary education levels, secondary education  
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35 levels, and college or higher education levels and tumour stages I, II and III.  
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40 Each patient using the French-LARS score will be asked to review the questionnaire by  
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42 precisely pointing out all the difficulties encountered when using the instrument, including  
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44 the following: items that are ambiguous or poorly formulated; difficulties or confusion  
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46 completing the scale. They will then be asked to indicate whether the questionnaire is  
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48 acceptable and easy to understand.  
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### 53 ***Reliability***

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55 Reproducibility will be investigated by a test-retest procedure. A randomly selected subgroup  
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57 of participants (n= 400) will be sent the French-LARS score questionnaire twice (figure 1).  
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3 The second test will be sent to the participants one or two weeks after completion of the first  
4 test. Patients will be asked if they have experienced any significant change in bowel function  
5 between the first and the second test. Those confirming a change in bowel function will be  
6 excluded from the test-retest analysis. Non-responders will be further contacted twice, either  
7 via postal invitation or by phone. The test-retest study will be performed by comparing the  
8 French-LARS scores obtained at the two time points. The test-retest reliability of the  
9 questionnaire will be assessed by Cohen's Kappa coefficient (no LARS, minor LARS and  
10 major LARS scores) or by intra-class correlation coefficient, ICC (quantitative LARS score).  
11 Internal consistency will be estimated by the Cronbach alpha coefficient.  
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### 26 ***Convergent validity***

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28 Convergent validity will be determined by computing the correlations between the French-  
29 LARS score and the EORTC QLQ-C30 and QLQ-CR29 domains [23], which have been  
30 globally accepted and widely used as valid instruments for measuring QoL. Thus, eligible  
31 patients will receive a postal invitation to complete the EORTC QLQ-C30 and QLQ-CR29  
32 along with the French-LARS scores. Furthermore, to study the convergent validity between  
33 qualitative measures of the LARS scores (no LARS, minor LARS and major LARS) and  
34 QoL, the patients will be asked a general question [16, 19]: "Overall, how much does your  
35 bowel function affect your quality of life?" Four mutually exclusive responses, "not at all",  
36 "very little", "somewhat" or "a lot", will be proposed.  
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### 51 ***Discriminant validity***

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53 Regarding the scoring instructions for these two instruments, a high score represents a high  
54 QoL or a high level of functioning for the global QoL subscale and functional subscale.  
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56 However, for a symptom subscale/item, the higher the score, the more severe the symptom.  
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3 The ability to discriminate between patients with different clinical characteristics is necessary  
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5 for an instrument to be considered valid. To test the tool's discriminant validity, we will use  
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7 known variables, including gender, age, neoadjuvant radiation therapy, distance of the  
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9 tumour from the anal verge, the extent of mesorectal excision (partial versus total), prior  
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11 temporary stoma, length of postoperative period (time since stoma-free rectal resection  
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13 surgery or reversal surgery from temporary stoma) and postoperative septic complications  
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15 such as pelvic abscess or anastomotic leakage. These variables are known to affect bowel  
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17 function after SPS in rectal cancer patients [11-13, 24]. The following numerical variables  
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19 will be changed into binary variables: age, distance of the tumour from the anal verge, and  
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21 length of the postoperative period. The median value for each will serve as the cut-off point.  
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23 Neoadjuvant radiation therapy, the extent of mesorectal excision (partial versus total), and  
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25 prior temporary stoma will be treated as dichotomous variables: no treatment at all versus  
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27 treatment. Moreover, interactions with neoadjuvant radiation therapy will be systematically  
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29 tested. The EORTC will provide us with and authorize our use of the French version of the  
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31 two questionnaires.  
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#### 40 ***Sensitivity of the items***

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42 A systematic search for ceiling or floor effects will be performed.  
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#### 47 ***Internal consistency***

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49 Internal consistency will be assessed using Cronbach's alpha coefficient.  
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#### 53 ***Internal validity***

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55 A factorial analysis will allow verification of the internal structure of the scale. The statistical  
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57 method used is described below.  
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### ***Confirmatory analysis***

A confirmatory analysis will be conducted to evaluate the recognized structural validity of the scale with regard to its first edition.

### ***Statistical analysis***

Quantitative variables will be expressed as the mean  $\pm$  standard deviation (SD), and qualitative variables will be expressed as the number of patients and percentages. The experimental design of the study leads to the same patient being seen several times during their oncology follow-up. However, apart from the subgroup of patients who participate in the study of repeatability, each patient will complete only one questionnaire in the study. Comparisons between the mean scores of the three groups (no LARS, minor LARS or major LARS) will be carried out with the help of an ANOVA or a Kruskal-Wallis test, depending on whether the data follow the verified homoscedasticity hypothesis or not. Post hoc comparisons will be performed with the Bonferroni correction or the Nemenyi test. Factor analysis will be performed with a principal component analysis. The selected factors will correspond to an eigenvalue  $\geq 1$ . The repeatability test (test-retest), in which 400 patients will be asked to complete the F-LARSF-LARSF-LARS twice within 15 days, will be Student's *t*-test for repeated measurements, with the help of the intraclass correlation coefficient (ICC) and its 95% CI, will use ANOVA for random effects models. After estimating the various components of the total variance, the ICC will be calculated in the usual manner. A Bland and Altman plot will be used to show the level of agreement of the repeatability test.

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3 The sensitivity and specificity of the French-LARS score in predicting the impact on QoL  
4 will be assessed by receiver operating characteristic (ROC) curves of the score versus groups  
5 reporting no/minor or some/major impact on QoL.  
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10 The correlation between the LARS validated score and the QLQ questionnaires (EORTC's  
11 QLQ-C30, QLQ-CR29) will be estimated with the Pearson correlation coefficient as well as  
12 with the Spearman correlation coefficient and its 95% CI.  
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17 The inclusion of the data indicating the impact of LARS on QoL will be based on a univariate  
18 approach and then a multivariate approach using ad hoc models according to the nature of the  
19 dependent variable (binary or multinomial logistic regression or linear regression depending  
20 on whether the QoL score is considered qualitative or quantitative). Only variables whose  
21 level of significance in the univariate analysis is  $p < 0.15$  will be included in the multivariate  
22 model. This approach will enable the identification of the risk factors linked to a deterioration  
23 in QoL and an evaluation of their impact.  
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28 Confirmatory analysis will use structural equation models that enable the validation of the  
29 measurement structure of various concepts.  
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33 All the tests will be two-sided with a level of significance ( $p$ ) that equals 0.05. IBM®-SPSS®  
34 22.0 and AMOS for Windows® software will be used.  
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### 37 38 39 40 41 42 ***Patient and public involvement***

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44 Patients were not involved in the design, the recruitment and conduct of the study. The  
45 results will be disseminated to study participants by email/paper by the physicians who  
46 included them in the study.  
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### 50 51 52 53 ***Feasibility***

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55 Thirty-four colorectal cancer centres, including both university hospitals and cancer control  
56 centres, have given their consent to include between 50 and 100 patients who underwent SPS  
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3 from 2007 to 2017 (see the list of participating centres in the Acknowledgements section).  
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5 The availability of patients for study inclusion from each GRECCAR centre has been  
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7 demonstrated in published randomized studies (25-28). We chose to include patients who  
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9 underwent SPS between 2007 and 2017 for two reasons. First, the French recommendations  
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11 for clinical practice and therapeutic choices for rectal cancer were published after 2007,  
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13 which make the diagnoses and therapeutic strategies homogeneous [10]. Second, participants  
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15 were approached a minimum of 24 months after surgery to allow their bowel function to have  
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17 regained stability [11, 18, 19]. Finally, eligible participants are usually monitored in each  
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19 centre at regular intervals to screen for local recurrence and/or distant metastasis. For all  
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21 these reasons, approximately 3000 patients will be contacted in order to include more than  
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23 1000 patients, expecting a 33% response rate.  
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### 30 ***Registration***

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32 The data will be collected and registered in e-CRFs by a dedicated local technical research  
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34 team using the Ennov Clinical software.  
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### 40 ***Study organization***

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42 The lead partner will be the University Hospital of Caen, France. The study will receive  
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44 financial support from the Program for Hospital Clinical Cancer Research “**INCa-**  
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46 **DGOS\_12112**”.  
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### 51 ***Duration and timeline***

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53 Patients will be included for 12 months. The approval protocol from the ethical committee,  
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55 financial support, and e-CRFs were developed in 2018 and 2019. Recruitment of the patients  
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57 is planned to continue until the first semester of 2021. The database will be closed in 2021,  
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3 after which data analysis, manuscript writing, and submission for publication will follow  
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5 (figure 2).  
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### 10 ***Ethics***

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12 The institutional review board of the University Hospital of Caen and the ethics committee  
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14 (CPP Nord Ouest I, January 25, 2019) approved the study. The French-LARS study was  
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16 registered on January 28, 2019, on the ClinicalTrials.gov Web site with trial identification  
17  
18 number NCT03569488. This study is supported by a grant from the French Ministry of  
19  
20 Health (PHRC- K17-031). The institutional promoter is the University Hospital of Caen  
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22 Department of Clinical Research and Innovation (DCRI).  
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### 28 **Discussion**

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30 Although the prevalence and severity of LARS remain difficult to assess, the LARS score,  
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32 which has been developed and validated for seven years, represents the best questionnaire to  
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34 capture anorectal postoperative function to date [15]. However, a validated French version of  
35  
36 the LARS score is not yet available. This French-LARS score will allow for the development  
37  
38 of future research and clinical practice in France. LARS remains a major problem, but it is  
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40 not well understood among healthcare professionals, and it is frequently underestimated.  
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42 Furthermore, there is considerable discrepancy between the clinician's judgement of patient  
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44 perception and the patient's actual view or experience [25, 26]. For example, specialists tend  
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46 to overestimate the impact of incontinence and frequent bowel movements, while they  
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48 underestimate the impact or urgency and clustering [25]. Therefore, knowledge of therapeutic  
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50 options such as transanal irrigation, biofeedback, or sacral nerve stimulation for patients with  
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52 LARS is limited [27-29]. These recent studies have indicated that there is a need for  
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54 improved LARS education for clinicians [25, 26]. There is now evidence that both the  
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3 distribution of patients within different LARS groups (minor and/or major) and the impact of  
4 LARS on QoL do not change over time [30]. According to recent studies [31], nearly 50% of  
5 patients still experience major LARS 13 to 15 years after surgery. Interestingly, only major  
6 LARS has an impact on patients' QoL [32].  
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12 A 2019 survey highlights the notable functional consequences reported by RC survivors after  
13 SPS surgery [33]. Based on validated instruments, 40% of RC survivors suffer from a major  
14 LARS episode that significantly impairs their QoL. More interestingly, bowel dysfunction  
15 was the only predictor of QoL for such patients after adjustment for age and various QoL  
16 components (urinary and sexual function) [33].  
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22 Clinicians will be able to use the validated French LARS score in daily clinical practice not  
23 only to identify patients with elevated LARS scores but also to predict bowel dysfunction for  
24 prevention and rapid management. It will hopefully lead to improved clinician awareness in  
25 order to improve both the prevention and treatment of bowel dysfunction and the information  
26 given to patients. In the future, we will be able to develop a new patient-led follow-up  
27 programme based on symptom burden and health-related QoL. To this end, a recently  
28 published nomogram, "the POLARS score", has been developed to predict bowel dysfunction  
29 severity prior to anterior resection [34]. Theoretically, it allows clinicians to personalize care  
30 during multidisciplinary team meetings, to prepare patients for the consequences of  
31 treatment, and to guide the treatment decision with patient consent. An alternative strategy  
32 for high-risk patients, called the "watch-and-wait" policy, has been proposed in cases of  
33 complete clinical response following chemo-radiation therapy. Although it leads to fewer  
34 functional problems than rectal resection, major LARS symptoms have been reported in up to  
35 one-third of these patients [35]. However, there is, to date, insufficient evidence to draw firm  
36 conclusions about the oncological safety of this approach.  
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3 In summary, the validation of the French-LARS score will allow the use of a scientific  
4 instrument to assess both the prevalence and severity of LARS. Together with oncological  
5 data, it will also form a basis on which to discuss functional outcomes with patients.  
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### List of abbreviations

C30: Core 30

CR 29: Colo Rectal 29

CRF: Case Report Form

DCRI: Department of Clinical Research and Innovation

eCRF: electronic Case Report Form

EORTC: European Organization for Treatment and Research of Cancer

FSFI: Female Sexual Function Index

ICC: Intraclass Correlation Coefficient

QLQ: Quality of Life Questionnaire

LARS: Low Anterior Resection Syndrome

MSKCC: Memorial Sloan Kettering Cancer Center

PME: Partial Mesorectal Excision

POLARS: Pre-Operative Low Anterior Resection Syndrome

QoL: Quality of Life

RC: Rectal Cancer

SD: Standard Deviation

SPS: Sphincter-preserving surgery

TME: Total Mesorectal Excision

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16 Study conception and design: AA, VB, RM, YE. Intervention design: RM, AA, VB, YE, JJD,  
17  
18 FC, YC, JJD, BM and YE. Analysis of data will be done by YE, OD and RM.  
19

20  
21 AA drafted the work, which was revised critically for intellectual content by TJ. All authors  
22  
23 gave final approval of this version to be published.  
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34  
35 None declared.  
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3 Figure legend  
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5 Figure 1. Consort diagram: Flow of participants throughout study  
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8 Figure 2 - Forecasting steps adapted to the study  
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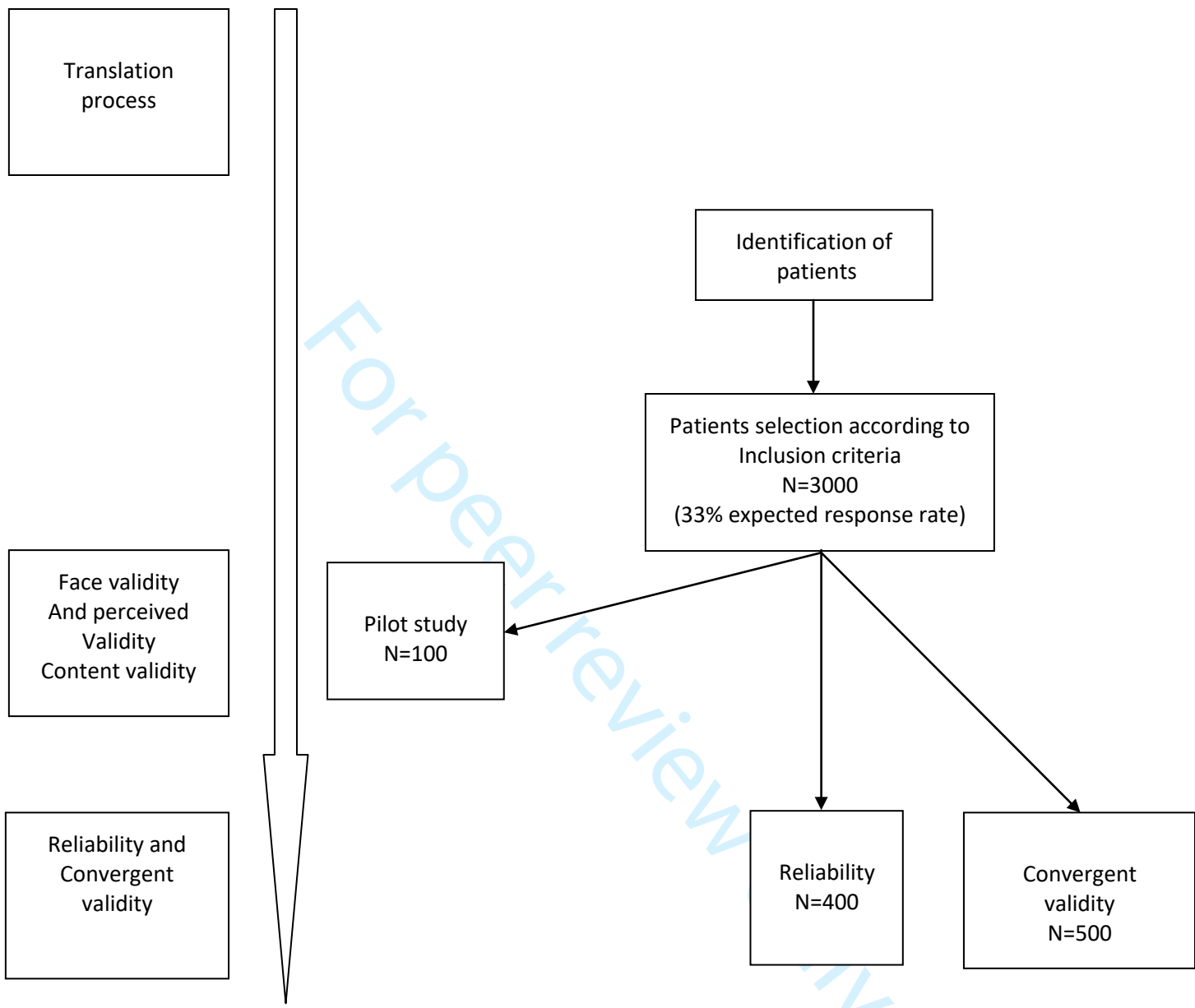


Figure 1. Consort diagram: Flow of participants throughout study

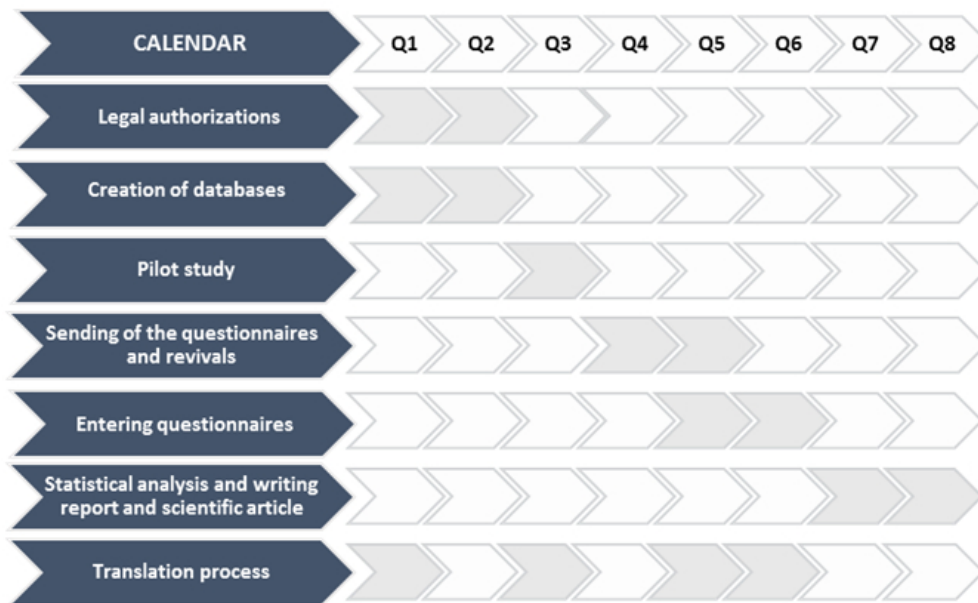


Figure 2 - Forecasting steps adapted to the study

57x34mm (300 x 300 DPI)

# BMJ Open

## **“The French LARS score”: Validation of the French version of the low anterior resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients: a study protocol**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034251.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Jan-2020
Complete List of Authors:	Eid, Yassine; Centre Hospitalier Universitaire de Caen, digestive surgery; UMRS 1086, Bouvier, Véronique; Cancers et préventions Dejardin , Olivier; Cancers et préventions Menahem, Benjamin; Centre Hospitalier Universitaire de Caen Chaillot, Fabien; Centre Hospitalier Universitaire de Caen Chene, Yannick; Centre Hospitalier Universitaire de Caen Dutheil, Jean Jacques; Centre Hospitalier Universitaire de Caen Juil, Therese; Aarhus Univ Hosp Morello, Rémy; Centre Hospitalier Universitaire de Caen Alves, Arnaud; Centre Hospitalier Universitaire de Caen
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery
Keywords:	bowel dysfunction, rectal cancer, low anterior resection syndrome, colorectal functional outcome, quality of life, validation

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3 **“The French LARS score”: Validation of the French version of the low anterior**  
4 **resection syndrome (LARS) score for measuring bowel dysfunction after sphincter-**  
5 **preserving surgery among rectal cancer patients: a study protocol**  
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12 Eid Y <sup>1,2,3</sup>, Bouvier V <sup>2,4</sup>, Dejardin O <sup>2,3</sup>, Menahem B<sup>1</sup>, Chaillot F<sup>3</sup>, Chene Y<sup>3</sup>, Dutheil JJ<sup>3</sup>,  
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## Abstract

**Introduction.** Many bowel problems following low anterior resection (LAR) for rectal cancer considerably impair the quality of life (QoL) of patients. The LAR Syndrome (LARS) scale is a self-report questionnaire to identify and assess bowel dysfunction after rectal cancer surgery. It has been translated and validated in several languages but not in French (metropolitan French). The primary objective is to adapt the LARS scale to the French language (called French-LARS score) and to assess its psychometric properties. Secondary objectives are to assess both the prevalence and severity of LARS and to measure their impact on QoL.

**Method and analysis.** A French multicentre observational cohort study has been designed. The validation study will include translation of the LARS scale following the current international recommendations, assessment of its reliability, convergent and discriminant validities, sensitivity, internal consistency, internal validity, and confirmatory analyses. One thousand patients will be enrolled for the analyses. The questionnaire will be initially administered to the first 100 patients in order to verify the adequacy and degree of comprehension of the questions. Then reproducibility will be investigated by a test-retest procedure in the following 400 patients.

An analysis will be conducted to determine the correlation between the LARS score and the QLQ questionnaires (EORTC's QLQ-C30, QLQ-CR29). Risk factors linked to QoL deterioration will be identified and their impact will be measured. This study will meet the need for a validated tool to improve patient care and QoL.

**Ethics and dissemination.** The institutional review board of the University Hospital of Caen and the ethics committee (CPP Nord Ouest I, January 25, 2019) approved the study. This study is supported by a grant from the French Ministry of Health (PHRC- K17-031). The

1  
2  
3 institutional promoter is the University Hospital of Caen Department of Clinical Research  
4  
5 and Innovation (DCRI).  
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8 **Trial registration number.** NCT03569488  
9

10 **Strengths and limitations of this study.**  
11

12 - The validation of the French version of the LARS score (the French-LARS score) will allow  
13 the use of a scientific instrument to assess both the prevalence and severity of LARS in  
14 French language.  
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16  
17 - The French-LARS study is a multicentre cohort study of rectal cancer patients  
18 included from 34 units of colorectal surgery in France.  
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21 - Limitations include the use of non-probability sampling, which is expected to impose  
22 selection bias.  
23

24 **Word count of the manuscript: 4411 words**  
25

26 **Keywords:** bowel dysfunction, rectal cancer, low anterior resection syndrome, colorectal  
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28 functional outcome, quality of life, validation  
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## Manuscript

### Background

#### *Rectal cancer management*

In recent years, progress in the multimodal treatments of rectal cancer (RC) has improved local disease control and increased the survival rate (up to 50% survival at 5 years) [1, 2]. At the same time, the evolution of surgical techniques and the achievement of a 1-cm distal margin below the tumour have pushed back the limits of sphincter-preserving surgery (SPS) without impairing oncological prognosis [3, 4]. Up to 80% of patients with RC undergo SPS [5]. The assessment of RC outcome has traditionally focused on morbidity rate, tumour recurrence and survival, while functional sequelae (i.e., bowel and/or genitourinary impairment) have long been regarded as inherent to the nature of RC treatments [6, 7]. However, with improved surgical outcomes, we and others have observed a rising number of RC survivors who live with numerous potential side-effects and, eventually, an impaired quality of life (QoL) [6-9]. Therefore, bowel function, like QoL, has become an increasingly important focus of care [10].

#### *Bowel dysfunction following SPS*

It is widely accepted that as many as 50% to 90% of patients who undergo SPS will have a subsequent change in bowel habit [11, 12]. The wide spectrum of bowel symptoms after resection with SPS has been termed the "low anterior resection syndrome (LARS)". The prevalence and severity of LARS remain difficult to assess. Several authors still consider faecal incontinence to be the foremost intestinal sequela, underscoring the impact of urgency and impaired evacuation.

LARS is defined as follows: frequent bowel movements (increased number of stools during the day and/or night); clustering (repeated passage of several stools over a few hours, sometimes requiring the patient to defecate four or five times in 1–2 h); disorders of

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3 continence from minimal gas leaks or staining to debilitating faecal incontinence and faecal  
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5 urgency; and urgency (inability to prevent defecation for > 15 min when the need arises) [11,  
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7 12]. These symptoms usually appear immediately after surgery, become most pronounced  
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9 during the first few months, improve somewhat thereafter, and reach a steady state after  
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11 approximately one to two years [11, 12]. Recently, a pragmatic definition of LARS has been  
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13 proposed: "disordered bowel function after rectal resection, leading to a detriment in QOL"  
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15 [13].  
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### 22 ***Rationale for using the LARS score***

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24 Although many questionnaires or instruments have been used to assess the impact of LARS  
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26 on QoL, a recent systematic review and meta-analysis observed that 65% of the studies  
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28 included did not use a validated assessment instrument [14]. Furthermore, there is a wide  
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30 range of assessment tools, including single examinations and different scoring systems, such  
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32 as the Memorial Sloan Kettering Cancer Center (MSKCC) score, the bowel function  
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34 instrument (BFI), and the Wexner, St. Marks and FSFI scores. Most of the instruments used  
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36 to assess bowel function measure faecal incontinence but leave aside other symptoms that  
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38 have been shown to have a more significant correlation with QoL, such as clustering and  
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40 urgency [15]. Since 2012, a group of Danish authors has developed and validated a 5-item  
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42 instrument for the evaluation of LARS: the LARS score [16]. The items are incontinence for  
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44 flatus or for liquid stool, frequency of bowel movements, clustering of stools, and urgency. It  
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46 allows the categorization of patients into three groups: no LARS (0-20 points), minor LARS  
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48 (21-29 points), and major LARS (30-42 points) [16]. To date, it is the best questionnaire for  
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50 capturing anorectal postoperative function. When faecal incontinence is the major concern,  
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52 the Wexner, St. Marks or FSFI scores are adequate, the latter being the most sound from a  
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54 methodological viewpoint. While the MSKCC-FBI is the best questionnaire for evaluating  
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3 LARS, its use is complex. For this reason, the LARS score is currently used preferentially for  
4 first-line evaluation [15]. Its ability to reflect the impact of bowel dysfunction on QoL was  
5 proven in its initial validation and subsequently through its association with the EORTC  
6 QLQ-C30 scale [17]. In clinical settings, its severity categories (No LARS, Minor LARS, and  
7 Major LARS) can facilitate rapid identification of patients most in need of treatment. Patients  
8 with major LARS reported seriously compromised QoL and significantly worse QoL  
9 compared with those with No/Minor LARS. Consequently, half of the patients restricted their  
10 diet and limited their social activity [17]. In addition to the original Danish version, the  
11 LARS score has been translated into English, Dutch, Swedish, Spanish, German and Chinese,  
12 and can potentially be used widely[18-20].  
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### 29 *Hypothesis and objectives of the investigations*

30 Both the adoption of a uniform definition of LARS and the consistent use of the same  
31 questionnaire allow researchers to pool and compare the results of different studies and  
32 institutions. . However, a validated French version of the LARS score is not yet available.  
33 The main objective therefore will be to adapt and validate the LARS scale questionnaire to  
34 the French language (called French-LARS score) and assess its psychometric properties.  
35 Secondary objectives are to assess both the prevalence and severity of LARS and to measure  
36 their impact on QoL.  
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### 49 **Methods**

#### 50 51 52 53 *Study design*

54 The French-LARS study is an observational, multicentre, cohort study of rectal cancer  
55 patients who have undergone curative sphincter-preserving surgery with partial or total  
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mesorectal excision. Patients are included from 34 units of colorectal surgery in France (see list of participating centres in the Acknowledgements section). The study has been approved by the scientific board of the French Research Group of Rectal Cancer Surgery (GRECCAR). This group was created by surgical teams in France who are involved in the management of rectal cancer, with the aim of conducting and publishing multicentre clinical trials on the subject in high-level journals and expanding this surgical specialty to various learned societies. Most of the participating teams in the study are affiliated with the GRECCAR. All investigators will proceed with this study in accordance with the Declaration of Helsinki.

### ***Study population***

All patients will provide written informed consent prior to their enrolment for study participation.

The inclusion criteria are as follows: aged between 18 and 80 years (octogenarians were excluded because they suffer from significant comorbidities that exclude them from the majority clinical trials, they experience worse physical functioning compared to younger patients and third very few data are available about bowel function in octogenarians following rectal resection with nerve-sparing); rectal cancer patients who have undergone curative sphincter-preserving surgery with partial or total mesorectal excision; surgery performed between January 2007 and January 2017, with reversal of the defunctioning stoma before January 2017; bowel continuity restored for at least 24 months (including the reversal of the temporary stoma); voluntary participation in the study. The exclusion criteria are as follows: a palliative rectal cancer resection; presence of stoma; known disseminated or recurrent disease; cognition and/or language issues.

For patients lost to follow-up, an active search will be carried out with general practitioners and, if necessary, with the birth councils in order to know the vital status. Participants in the



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3 validation study will be identified through local databases by the investigators at each of the  
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5 participating centres. They will be selected randomly from the pool of eligible subjects.  
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8 Participants will be approached not earlier than 24 months after surgery to allow their bowel  
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10 function to have regained stability [11, 12, 17].  
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### 14 ***Data collected***

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16 Demographic and clinical information will be obtained from the databases. Patient  
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18 characteristics will be collected on e-CRFs (electronic Case Report Forms) and include age,  
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20 sex, body mass index, tumour height (distance from anal verge on MRI or rigid  
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22 sigmoidoscopy in centimetres), timing and type of neoadjuvant radiotherapy and  
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24 chemotherapy, if recommended; time since surgery; type of surgery (PME or TME); type of  
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26 anastomosis; defunctioning stoma; and postoperative mortality and morbidity such as pelvic  
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28 abscess, anastomotic leakage, and reoperation. Morbidity will be evaluated with the new  
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30 classification of surgical complications by Dindo et al. [21], which includes five grades. The  
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32 usual data will be recorded: distal and circumferential margins, the number of resected and  
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34 invaded nodes, tumoral differentiation, the presence of vascular emboli (venous or lymphatic,  
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36 intra- or extra-mural), perineural invasion, and the quality of the mesorectal excision. The  
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38 resected specimen will be staged according to American Joint Committee on Cancer (AJCC)  
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40 criteria (7th version).  
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46 Data collection will be performed according to the following procedures. (i) The researchers  
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48 will identify eligible participants by reviewing the medical records of rectal cancer patients.  
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50 (ii) Eligible patients will be contacted by postal invitation and will be informed about the  
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52 purpose of the study. (iii) The completed questionnaires will be carefully checked by the  
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54 researchers for any missing information. Eligible patients will be contacted by postal  
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56 invitation twice if they do not reply. Any unclear item of missing information will be  
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3 reconfirmed through a phone call. If this is not possible, the questionnaire will be considered  
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5 invalid.  
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### 10 ***Study endpoints***

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12 The primary objective is to validate a French-language version of the LARS score, to adapt  
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14 the LARS scale questionnaire to the French language (called French-LARS score) and to  
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16 assess its psychometric properties and factor structure. The secondary objectives are to assess  
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18 both the prevalence and severity of LARS and to measure their impact on QoL.  
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### 23 ***Detailed description of implemented techniques***

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25 The validation study of the French version of the LARS score is based on face and content  
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27 validity as well as on the measurement of its psychometric properties, in compliance with the  
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29 standards published by the American Educational Research Association et al. [22].  
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### 34 ***Validation study of French version***

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36 The different steps are detailed in figure 1 and figure 2.  
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### 40 ***Translation process***

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42 After obtaining permission from the original authors [18, 19], we will conduct the forward-  
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44 and back-translation procedures in accordance with the translation guidelines provided by the  
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46 authors. The French-LARS questionnaire will be developed by translating the questions into  
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48 French, a task that will be performed by two independent translators who are native French  
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50 speakers with a high level of fluency. The two translators will check and discuss the two  
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52 translations only for inconsistency and will establish a single preliminary French version.  
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54 Thereafter, the French version will be back-translated into English by two independent  
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56 professional translators; both are fluent in French and with English as their mother tongue,  
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3 and both are unfamiliar with the background objectives of the study. Both versions of the  
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5 backward translation will be compared with each other and with the initial version. After  
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7 minor adjustments, a final French version will be agreed upon. The final French version and  
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9 the whole translation process mentioned above will be sent to the original authors for  
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11 approval.  
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### 14 15 16 17 ***Content validity***

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19 Content validity will be assessed by a panel of experts during the process, which will lead to  
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21 the final French version of the scale. Using a 3-point Likert scale (poor, average and good),  
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23 each expert will judge independently whether the content from the original LARS score is  
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25 conserved and adapted in the French language (see Acknowledgements).  
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### 30 31 ***Face validity and perceived validity***

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33 Then, a pilot study will be conducted. The French LARS score will be administered to 100  
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35 patients in order to verify the adequacy and degree of comprehension of the questions (figure  
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37 1). These patients will be chosen according to their representativeness based on a wide range  
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39 of socio-demographic and clinical characteristics. Both male and female patients will  
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41 complete the questionnaire. They will have primary education levels, secondary education  
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43 levels, and college or higher education levels and tumour stages I, II and III.  
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47 Each patient using the French-LARS score will be asked to review the questionnaire by  
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49 precisely pointing out all the difficulties encountered when using the instrument, including  
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51 the following: items that are ambiguous or poorly formulated; difficulties or confusion  
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53 completing the scale. They will then be asked to indicate whether the questionnaire is  
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55 acceptable and easy to understand.  
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### ***Reliability***

Reproducibility will be investigated by a test-retest procedure. A randomly selected subgroup of participants (n= 400) will be sent the French-LARS score questionnaire twice (figure 1).

The second test will be sent to the participants one or two weeks after completion of the first test. Patients will be asked if they have experienced any significant change in bowel function between the first and the second test. Those confirming a change in bowel function will be excluded from the test-retest analysis. Non-responders will be further contacted twice, either via postal invitation or by phone. The test-retest study will be performed by comparing the French-LARS scores obtained at the two time points. The test-retest reliability of the questionnaire will be assessed by Cohen's Kappa coefficient (no LARS, minor LARS and major LARS scores) or by intra-class correlation coefficient, ICC (quantitative LARS score). Internal consistency will be estimated by the Cronbach alpha coefficient.

### ***Convergent validity***

Convergent validity will be determined by computing the correlations between the French-LARS score and the EORTC QLQ-C30 and QLQ-CR29 domains [23], which have been globally accepted and widely used as valid instruments for measuring QoL. Thus, eligible patients will receive a postal invitation to complete the EORTC QLQ-C30 and QLQ-CR29 along with the French-LARS scores. Furthermore, to study the convergent validity between qualitative measures of the LARS scores (no LARS, minor LARS and major LARS) and QoL, the patients will be asked a general question [16, 19]: "Overall, how much does your bowel function affect your quality of life?" Four mutually exclusive responses, "not at all", "very little", "somewhat" or "a lot", will be proposed.

### ***Discriminant validity***

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3 Regarding the scoring instructions for these two instruments, a high score represents a high  
4 QoL or a high level of functioning for the global QoL subscale and functional subscale.  
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6 However, for a symptom subscale/item, the higher the score, the more severe the symptom.  
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8 The ability to discriminate between patients with different clinical characteristics is necessary  
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10 for an instrument to be considered valid. To test the tool's discriminant validity, we will use  
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12 known variables, including gender, age, neoadjuvant radiation therapy, distance of the  
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14 tumour from the anal verge, the extent of mesorectal excision (partial versus total), prior  
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16 temporary stoma, length of postoperative period (time since stoma-free rectal resection  
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18 surgery or reversal surgery from temporary stoma) and postoperative septic complications  
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20 such as pelvic abscess or anastomotic leakage. These variables are known to affect bowel  
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22 function after SPS in rectal cancer patients [11-13, 24]. The following numerical variables  
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24 will be changed into binary variables: age, distance of the tumour from the anal verge, and  
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26 length of the postoperative period. The median value for each will serve as the cut-off point.  
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28 Neoadjuvant radiation therapy, the extent of mesorectal excision (partial versus total), and  
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30 prior temporary stoma will be treated as dichotomous variables: no treatment at all versus  
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32 treatment. Moreover, interactions with neoadjuvant radiation therapy will be systematically  
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34 tested. The EORTC will provide us with and authorize our use of the French version of the  
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36 two questionnaires.  
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### ***Sensitivity of the items***

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48 A systematic search for ceiling or floor effects will be performed.  
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### ***Internal consistency***

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54 Internal consistency will be assessed using Cronbach's alpha coefficient.  
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### ***Internal validity***

A factorial analysis will allow verification of the internal structure of the scale. The statistical method used is described below.

### ***Confirmatory analysis***

A confirmatory analysis will be conducted to evaluate the recognized structural validity of the scale with regard to its first edition.

### ***Statistical analysis***

Quantitative variables will be expressed as the mean  $\pm$  standard deviation (SD), and qualitative variables will be expressed as the number of patients and percentages. The experimental design of the study leads to the same patient being seen several times during their oncology follow-up. However, apart from the subgroup of patients who participate in the study of repeatability, each patient will complete only one questionnaire in the study. Comparisons between the mean scores of the three groups (no LARS, minor LARS or major LARS) will be carried out with the help of an ANOVA or a Kruskal-Wallis test, depending on whether the data follow the verified homoscedasticity hypothesis or not. Post hoc comparisons will be performed with the Bonferroni correction or the Nemenyi test. Factor analysis will be performed with a principal component analysis. The selected factors will correspond to an eigenvalue  $\geq 1$ .

The repeatability test (test-retest), in which 400 patients will be asked to complete the F-LARSF-LARSF-LARS twice within 15 days, will be Student's *t*-test for repeated measurements, with the help of the intraclass correlation coefficient (ICC) and its 95% CI, will use ANOVA for random effects models. After estimating the various components of the

total variance, the ICC will be calculated in the usual manner. A Bland and Altman plot will be used to show the level of agreement of the repeatability test.

The sensitivity and specificity of the French-LARS score in predicting the impact on QoL will be assessed by receiver operating characteristic (ROC) curves of the score versus groups reporting no/minor or some/major impact on QoL.

The correlation between the LARS validated score and the QLQ questionnaires (EORTC's QLQ-C30, QLQ-CR29) will be estimated with the Pearson correlation coefficient as well as with the Spearman correlation coefficient and its 95% CI.

The inclusion of the data indicating the impact of LARS on QoL will be based on a univariate approach and then a multivariate approach using ad hoc models according to the nature of the dependent variable (binary or multinomial logistic regression or linear regression depending on whether the QoL score is considered qualitative or quantitative). Only variables whose level of significance in the univariate analysis is  $p < 0.15$  will be included in the multivariate model. This approach will enable the identification of the risk factors linked to a deterioration in QoL and an evaluation of their impact.

Confirmatory analysis will use structural equation models that enable the validation of the measurement structure of various concepts.

All the tests will be two-sided with a level of significance ( $p$ ) that equals 0.05. IBM®-SPSS® 22.0 and AMOS for Windows® software will be used.

### ***Patient and public involvement***

Patients were not involved in the design, the recruitment and conduct of the study. The results will be disseminated to study participants by email/paper and to the physicians who included them in the study.

### ***Feasibility***

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3 Thirty-four colorectal cancer centres, including both university hospitals and cancer control  
4 centres, have given their consent to include between 50 and 100 patients who underwent SPS  
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6 from 2007 to 2017 (see the list of participating centres in the Acknowledgements section).  
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10 The availability of patients for study inclusion from each GRECCAR centre has been  
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12 demonstrated in published randomized studies (25-28). We chose to include patients who  
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14 underwent SPS between 2007 and 2017 for two reasons. First, the French recommendations  
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16 for clinical practice and therapeutic choices for rectal cancer were published after 2007,  
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18 which make the diagnoses and therapeutic strategies homogeneous [10]. Second, participants  
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20 were approached a minimum of 24 months after surgery to allow their bowel function to have  
21  
22 regained stability [11, 18, 19]. Finally, eligible participants are usually monitored in each  
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24 centre at regular intervals to screen for local recurrence and/or distant metastasis. For all  
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26 these reasons, approximately 3000 patients will be contacted in order to include more than  
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28 1000 patients, expecting a 33% response rate.  
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### 35 ***Registration***

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37 The data will be collected and registered in e-CRFs by a dedicated local technical research  
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39 team using the Ennov Clinical software.  
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### 44 ***Study organization***

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46 The lead partner will be the University Hospital of Caen, France. The study will receive  
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48 financial support from the Program for Hospital Clinical Cancer Research “**INCa-**  
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50 **DGOS\_12112**”.  
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### 56 ***Duration and timeline***



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3 Patients will be included for 12 months. The approval protocol from the ethical committee,  
4 financial support, and e-CRFs were developed in 2018 and 2019. Recruitment of the patients  
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6 is planned to continue until the first semester of 2021. The database will be closed in 2021,  
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8 after which data analysis, manuscript writing, and submission for publication will follow  
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12 (figure 2).  
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### 17 ***Ethics and dissemination***

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19 The institutional review board of the University Hospital of Caen and the ethics committee  
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21 (CPP Nord Ouest I, January 25, 2019) approved the study. The French-LARS study was  
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23 registered on January 28, 2019, on the ClinicalTrials.gov Web site with trial identification  
24  
25 number NCT03569488. This study is supported by a grant from the French Ministry of  
26  
27 Health (PHRC- K17-031). The institutional promoter is the University Hospital of Caen  
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29 Department of Clinical Research and Innovation (DCRI).  
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33 Results of this study will be disseminated by publication through peer-reviewed professional  
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35 and scientific journals. Participant data will be kept confidential and will not be shared with  
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37 the public. If there are requests for data sharing for appropriate research purposes, this will be  
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39 considered on an individual basis after trial completion and after the publication of the  
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41 primary manuscripts.  
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### 49 **Discussion**

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51 Although the prevalence and severity of LARS remain difficult to assess, the LARS score,  
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53 which has been developed and validated for seven years, represents the best questionnaire to  
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55 capture anorectal postoperative function to date [15]. However, a validated French version of  
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57 the LARS score is not yet available. This French-LARS score will allow for the development  
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3 of future research and clinical practice in France. LARS remains a major problem, but it is  
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5 not well understood among healthcare professionals, and it is frequently underestimated.  
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7 Furthermore, there is considerable discrepancy between the clinician's judgement of patient  
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9 perception and the patient's actual view or experience [25, 26]. For example, specialists tend  
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11 to overestimate the impact of incontinence and frequent bowel movements, while they  
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13 underestimate the impact of urgency and clustering [25]. Therefore, knowledge of therapeutic  
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15 options such as transanal irrigation, biofeedback, or sacral nerve stimulation for patients with  
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17 LARS is limited [27-29]. These recent studies have indicated that there is a need for  
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19 improved LARS education for clinicians [25, 26]. There is now evidence that both the  
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21 distribution of patients within different LARS groups (minor and/or major) and the impact of  
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23 LARS on QoL do not change over time [30]. According to recent studies [31], nearly 50% of  
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25 patients still experience major LARS 13 to 15 years after surgery. Interestingly, only major  
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27 LARS has an impact on patients' QoL [32].  
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33 A 2019 survey highlights the notable functional consequences reported by RC survivors after  
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35 SPS surgery [33]. Based on validated instruments and recent studies, 40% of RC survivors  
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37 suffer from major LARS symptoms at long-term follow-up that significantly impairs their  
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39 QoL. More interestingly, bowel dysfunction was the only predictor of QoL for such patients  
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41 after adjustment for age and various QoL components (urinary and sexual function) [33].  
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43 Clinicians will be able to use the validated French LARS score in daily clinical practice not  
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45 only to identify patients with elevated LARS scores but also to predict bowel dysfunction for  
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47 prevention and rapid management. It will hopefully lead to improved clinician awareness in  
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49 order to improve both the prevention and treatment of bowel dysfunction and the information  
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51 given to patients. In the future, we will be able to develop a new patient-led follow-up  
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53 programme based on symptom burden and health-related QoL. To this end, a recently  
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55 published nomogram, "the POLARS score", has been developed to predict bowel dysfunction  
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3 severity prior to anterior resection [34]. Theoretically, it allows clinicians to personalize care  
4 during multidisciplinary team meetings, to prepare patients for the consequences of  
5 treatment, and to guide the treatment decision with patient consent. An alternative strategy  
6 for high-risk patients, called the “watch-and-wait” policy, has been proposed in cases of  
7 complete clinical response following chemo-radiation therapy. Although it leads to fewer  
8 functional problems than rectal resection, major LARS symptoms have been reported in up to  
9 one-third of these patients [35]. However, there is, to date, insufficient evidence to draw firm  
10 conclusions about the oncological safety of this approach.  
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21 In summary, the validation of the French-LARS score will allow the use of a scientific  
22 instrument to assess both the prevalence and severity of LARS. Together with oncological  
23 data, it will also form a basis on which to discuss functional outcomes with patients.  
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**List of abbreviations**

C30: Core 30

CR 29: Colo Rectal 29

CRF: Case Report Form

DCRI: Department of Clinical Research and Innovation

eCRF: electronic Case Report Form

EORTC: European Organization for Treatment and Research of Cancer

FSFI: Female Sexual Function Index

ICC: Intraclass Correlation Coefficient

QLQ: Quality of Life Questionnaire

LARS: Low Anterior Resection Syndrome

MSKCC: Memorial Sloan Kettering Cancer Center

PME: Partial Mesorectal Excision

POLARS: Pre-Operative Low Anterior Resection Syndrome

QoL: Quality of Life

RC: Rectal Cancer

SD: Standard Deviation

SPS: Sphincter-preserving surgery

TME: Total Mesorectal Excision

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16 Study conception and design: AA, VB, RM, YE. Intervention design: RM, AA, VB, YE, JJD,  
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18 FC, YC, JJD, BM and YE. Analysis of data will be done by YE, OD and RM.  
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23 gave final approval of this version to be published.  
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### 33 ***Competing interests***

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5 Figure 1. Consort diagram: Flow of participants throughout study  
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8 Figure 2 - Forecasting steps adapted to the study  
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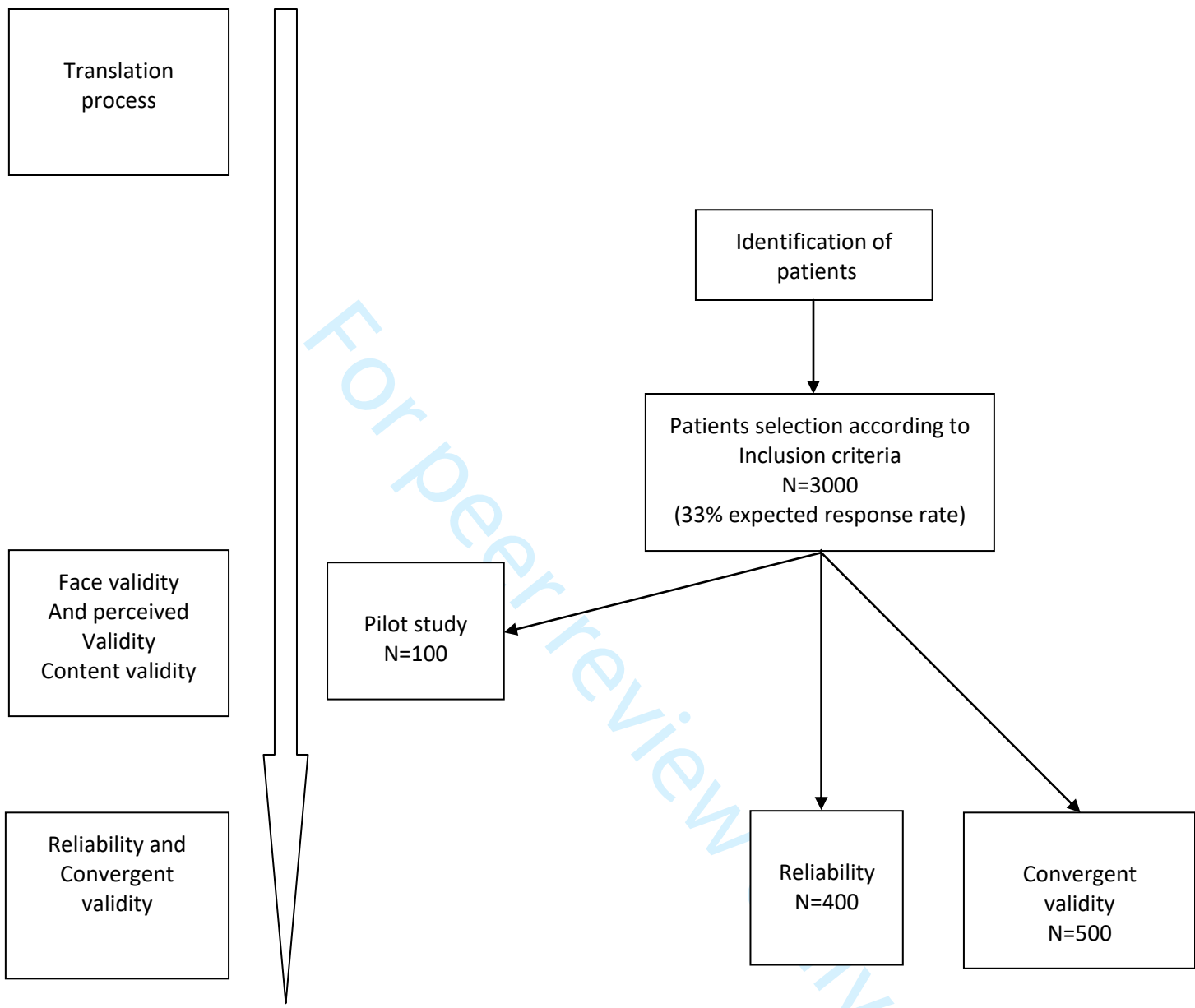


Figure 1. Consort diagram: Flow of participants throughout study

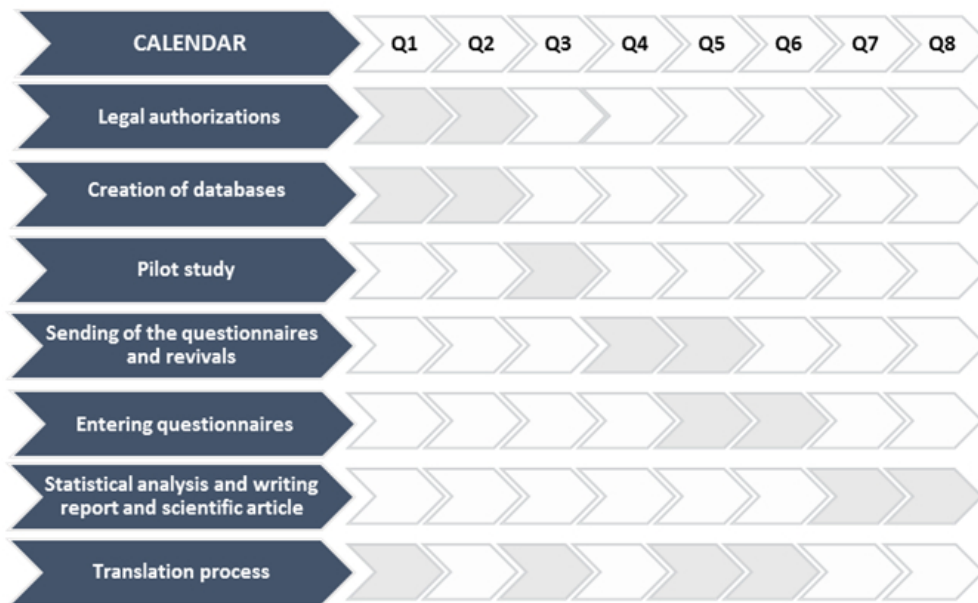


Figure 2 - Forecasting steps adapted to the study

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