

STUDY PROTOCOLS



A phase III randomized trial evaluating the quality of life impact of a tailored versus systematic use of defunctioning ileostomy following total mesorectal excision for rectal cancer—GRECCAR 17 trial protocol

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Abstract

Aim: The systematic use of a defunctioning ileostomy for 2–3 months postoperatively to protect low colorectal anastomosis (<7 cm from the anal verge) has been the standard practice after total mesorectal excision (TME). However, stoma-related complications can occur in 20%–60% of cases, which may lead to prolonged inpatient care, urgent reoperation and long-term definitive stoma. A negative impact on quality of life (QoL) and increased healthcare expenses are also observed. Conversely, it has been reported that patients without a defunctioning stoma or following early stoma closure (days 8–12 after TME) have a better functional outcome than patients with systematic defunctioning stoma in situ for 2–3 months.

Method: The main objective of this trial is to compare the QoL impact of a tailored versus systematic use of a defunctioning stoma after TME for rectal cancer. The primary outcome is QoL at 12 months postoperatively using the European Organization for Research and Treatment of Cancer QoL questionnaire QLQ-C30. Among 29 centres of the French GRECCAR network, 200 patients will be recruited over 18 months, with follow-up at 1, 4, 8 and 12 months postoperatively, in an open-label, randomized, two-parallel arm, phase III superiority clinical trial. The experimental arm (arm A) will undergo a tailored use of defunctioning stoma after TME based on a two-step process: (i) to perform or not a defunctioning stoma according to the personalized risk of anastomotic leak (defunctioning stoma only if modified anastomotic failure observed risk score ≥ 2) and (ii) if a stoma is fashioned, whether to perform an early stoma closure at days 8–12, according to clinical (fever), biochemical (C-reactive protein level on days 2 and 4 postoperatively) and radiological postoperative assessment (CT scan with retrograde contrast enema at days 7–8 postoperatively). The control arm (arm B) will undergo systematic use of a defunctioning stoma for 2–3 months after TME for all patients, in keeping with French national and international guidelines. Secondary outcomes will include comprehensive analysis of functional outcomes (including bowel, urinary and sexual function) again up to 12 months postoperatively and a cost

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analysis. Regular assessments of anastomotic leak rates in both arms (every 50 randomized patients) will be performed and an independent data monitoring committee will recommend trial cessation if this rate is excessive in arm A compared to arm B.

Conclusion: The GRECCAR 17 trial is the first randomized trial to assess a tailored, patient-specific approach to decisions regarding defunctioning stoma use and closure after TME according to personalized risk of anastomotic leak. The results of this trial will describe, for the first time, the QoL and morbidity impact of selective use of a defunctioning ileostomy and the potential health economic effect of such an approach.

KEYWORDS

ileostomy, quality of life, stoma, total mesorectal excision

INTRODUCTION

Management of rectal cancer has significantly evolved over the past two decades, in particular with the introduction of neoadjuvant therapy and standardized total mesorectal excision (TME) surgery which led to better cancer outcomes and a higher rate of sphincter-preserving restorative surgery [1–3]. In restorative surgery the most serious complications are pelvic sepsis and anastomotic leak (AL) [4]. The reported risk of AL following TME varies from 3% to 28% [5]. In the French randomized controlled trial (RCT) GRECCAR 5, AL was reported in 17.3% of cases [6]. Developing AL is associated with increased length of hospital stay and higher perioperative morbidity and mortality rate. AL is also associated with a higher chance of requiring a definitive stoma with associated patient care costs [7–9]. Longer term impact on oncological outcome, quality of life and survivorship are also reported [10–12].

The formation of a defunctioning ileostomy at the time of TME to ‘protect’ the anastomosis has become standard practice for anastomoses <7 cm from the anal margin. This is supported by RCT data that demonstrate lower rates of symptomatic AL (28.0% vs. 10.3%) and less clinically significant AL [13–17]. A Cochrane review and a meta-analysis have further demonstrated lower AL rates and reoperation rates in the setting of a defunctioning ileostomy [18, 19]. A recent nationwide study in the Netherlands [20] further demonstrated that ALs in the setting of a defunctioning ileostomy were more frequently Grade B anastomotic fistulas (requiring drainage) compared to Grade C (requiring reoperation) [20, 21]. French guidelines (updated in 2019) recommend systematic defunctioning stoma formation after TME with intraperitoneal anastomosis (approximately 7 cm from the anal margin), with a preference for ileostomy. Closure of stoma is recommended at 2–3 months post TME following preoperative assessment of the anastomosis by contrast enema and/or rectoscopy [22].

However, defunctioning ileostomy is not without risk and can also be associated with complications, although originally considered to be less significant than those of AL. Specific stoma-related complications include high output and electrolyte disturbance, skin complications and parastomal hernias, and a second procedure under general anaesthesia is required for closure of the stoma with the associated perioperative risks [23–29]. Furthermore, when stomas are

closed, anastomotic sequelae (including chronic pre-sacral sinuses and delayed or late AL) that were masked by the presence of the stoma can become apparent. In more recent times, we are gaining further insight into the medium to longer term risks associated with defunctioning ileostomy, including the impact on functional outcomes (in particular bowel function) and long-term sequelae of high output (e.g., chronic kidney disease); also a significant proportion are not closed [30]. There is also a significant cost to both patients and healthcare systems of long-term stomas [13, 27].

Balancing the risks versus the risk reduction offered by defunctioning ileostomy, it is reasonable to consider a more patient-centred approach so that those at high risk of AL benefit most from defunctioning ileostomy but low risk patients are not exposed to unnecessary morbidity. Furthermore, for those who may be of intermediate risk, can early closure of the stoma to reduce the risk of morbidity also be performed, that is, a tailored approach to stoma formation? A robust method for patient risk stratification, biochemically or based on patient and clinical characteristics, is required to pursue this approach. As previously highlighted, the overall rate of AL varies from 3% to 28% for low colorectal anastomosis. The rate can further vary from 6% to 50% depending on the AL risk factor profile of included patients [31]. AL risk factors can be considered as non-modifiable (e.g., gender, body mass index, neoadjuvant therapy and tumour size), modifiable (e.g., malnutrition, anaemia, hyperglycaemia, presence of sepsis) or related to surgical complexity (e.g., significant blood loss, number of staple fires required and duration of surgery). Modifiable risk factors can be optimized in most cases preoperatively and standardization of surgical training has improved the quality of surgical outcomes. Thus, non-modifiable factors remain as a differentiating factor for AL risk stratification.

In 2019, Penna et al. [31] reported how non-modifiable risk factors for AL can be used to risk stratify patients undergoing transanal TME and published the anastomotic failure observed risk (AFOR) score. The authors reported seven risk categories based on non-modifiable risk factors for AL with the associated observed AL rate for each category from the International Transanal TME Registry. The presence of each risk factor is given a score of 1 with diabetes receiving a score of 2. The associated risk of AL with cumulative AFOR score ranges from 6.3% with a score of 0 to 50.0% with a score of 6.

Prior to this RCT development, a feasibility study was performed. The first phase involved validating the internal validity of a modified AFOR (mAFOR) score in our patient population as a method of risk stratification and identifying a postoperative C-reactive protein (CRP) cut-off level or trend that could also differentiate the incidence of AL to support decision making regarding timing of stoma closure (in the press). It had previously been established that early closure of ileostomy both is safe and may offer improved bowel function [32–34]. The mAFOR score used tumour size following radiotherapy (RT) as follows: score of 0 if no RT was used or if tumour size at diagnosis was <25 mm and a score of 1 for tumour size >25 mm after RT (Table 1). A hundred patients treated from 2016 to 2018 were identified and the AL rate in this cohort was 17% (similar to national French data) [6]. The mAFOR score showed a good calibration with similar observed AL rates to that predicted. Furthermore, a CRP of 115 mg/l on postoperative day (POD) 2, decreasing (regardless of value) on POD 4, was also associated with not developing AL. In a second prospective analysis both mAFOR score and CRP were used for deciding on tailored stoma formation and the decision for early stoma closure. On analysis of 122 patients, a tailored stoma approach was associated with lower pelvic sepsis and AL rate and significantly better low anterior resection syndrome at 6 months postoperatively (in the press).

Our hypothesis is that a tailored approach incorporating avoiding a stoma, early stoma closure or standard defunctioning stoma use, where safe and appropriate, may reduce stoma-associated morbidity and improve functional outcomes and quality of life following TME for rectal cancer. To date, RCTs have supported a systematic blanket

approach to defunctioning stoma formation with AL as the primary outcome. GRECCAR 17 will be the first RCT to evaluate a tailored approach based on patient characteristics with early closure also evaluated based on both clinical, biochemical and radiological criteria that we have previously validated in our patient population [35]. Furthermore, it is the first RCT in this setting to use patient quality of life as a primary outcome.

METHOD

Trial design

GRECCAR 17 is a multicentre, open-label, two-parallel arm superiority randomized controlled phase III trial comparing the quality of life of a patient-tailored versus systematic use of defunctioning ileostomy in the 12 months following TME for rectal cancer (for colorectal anastomoses <7 cm from the anal margin). 'Tailored' describes decision making firstly to form either an ileostomy based on patient-specific risk of anastomotic failure and secondly to decide whether early ileostomy closure (PODs 8–12) is appropriate based on clinical, biochemical and radiological criteria (Figure 1).

Trial setting

This trial will take place in surgical departments with a special interest in colorectal surgery. All 29 French hospitals participating in the GRECCAR research group network will be eligible and invited to participate.

Eligibility criteria

An extensive list of eligibility criteria is summarized in [Table 2](#). Adult patients (>18 years old) are eligible to participate if they have histologically proven rectal cancer within 12 cm from the anal margin (confirmed by digital rectal examination or MRI). Patients who undergo minimally invasive (laparoscopic, robotic or transanal) TME (with or without neoadjuvant therapy) with an anastomosis <7 cm from the anal margin will be included.

Patients undergoing open TME, emergency surgery or requiring a diverting colostomy will be excluded. Further exclusion criteria will include preoperative pelvic sepsis, tumour-related perforation, requirement for a beyond TME excision or pelvic exenteration and biochemical malnutrition defined as albumin $<34\text{g/l}$ or prealbumin $<0.14\text{g/l}$. Patients with preoperative anaemia (defined as Hb $<10\text{g/dl}$) can be included once the anaemia is corrected preoperatively. Patients must be willing and capable of providing written informed consent and must be willing to comply with scheduled visits, treatment plans, laboratory tests and other trial-related procedures.

TABLE 1 Criteria for calculation of the modified anastomotic failure observed risk (mAFOR) score with the associated risk of anastomotic leak.

Risk factors for calculating the modified anastomotic failure observed risk score (mAFOR score)		
	Low risk	High risk
Gender	Female—0	Male—1
Body mass index	<30 kg/m ² —0	≥30 kg/m ² —1
Smoking	No—0	Yes—1
Diabetes	No—0	Yes—2
Tumour Size after CRT	≤25 mm—0	>25 mm—1

Cumulative score and associated AL risk
0 → 6.3%
1 → 10.7%
2 → 17.8%
3 → 23.3%
4 → 26.2%
5 → 33.3%
6 → 50.0%

Abbreviation: AL, anastomotic leak; CRT, chemoradiotherapy.

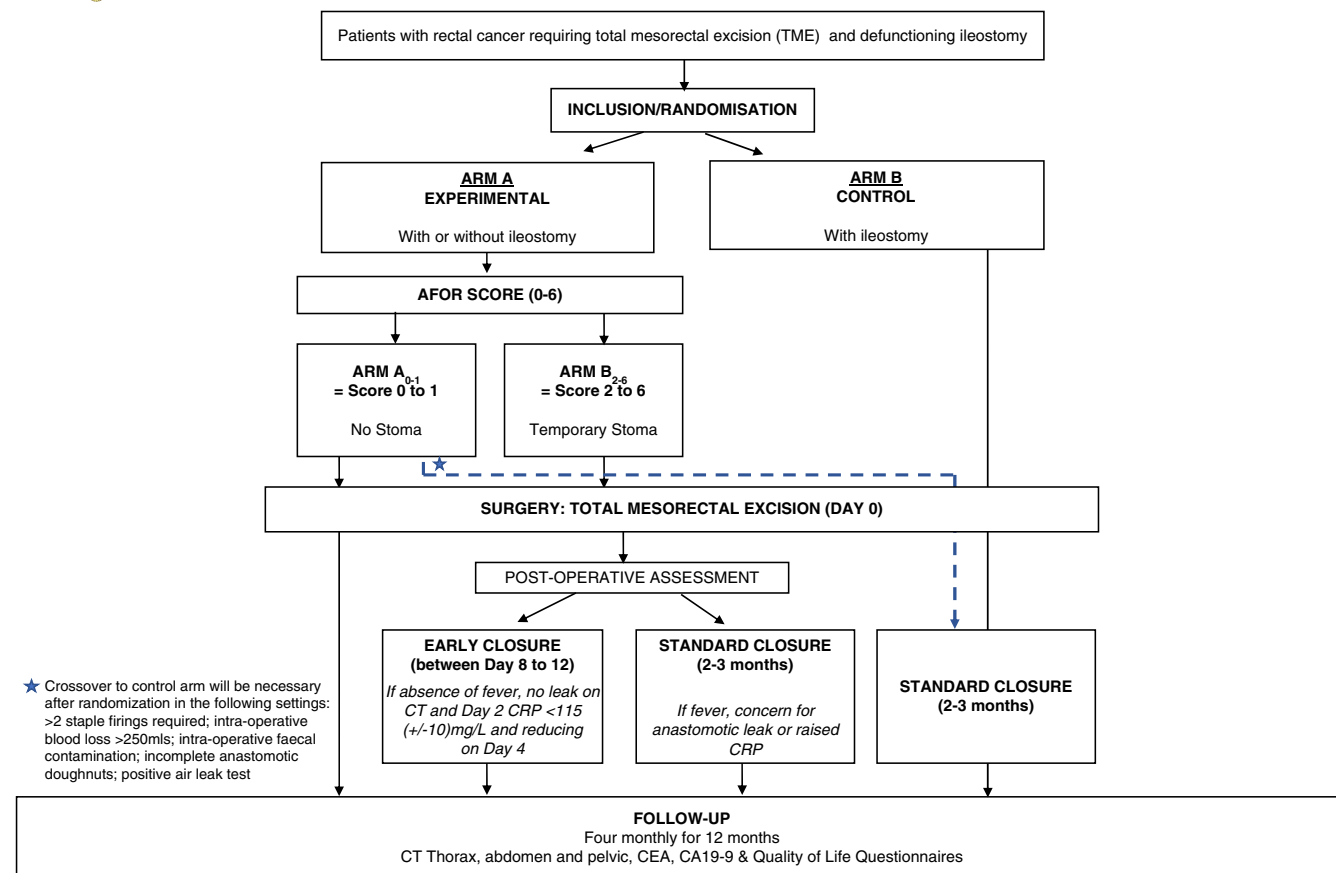


FIGURE 1 Trial design. CEA, carcinoembryonic antigen; CRP, C-reactive protein; TME, total mesorectal excision

Recruitment and randomization

Eligible patients will be identified at multidisciplinary meetings and preoperative clinic attendances where they will be invited to participate in the trial. All participants identified as suitable for inclusion will be provided with a detailed written patient information sheet and have a face-to-face discussion with a member of the research team. If happy to proceed they will be requested to provide written informed consent. Following receipt of written informed consent and confirmation of suitability for inclusion randomization will be carried out centrally via a secure internet facility (electronic data collection notebook using RedCap software). The randomization list will be established by the statistician of the Clinical Epidemiology Unit of the Bordeaux University Hospital before study commencement. The number of participants in each of the two randomized arms will be balanced in a 1:1 ratio. The experimental arm will be further stratified based on each patient's mAFOR score in two categories (0–1 and 2–6). A document describing the randomization procedure will be kept confidentially at the Clinical Epidemiology Unit.

Trial interventions

Treatment will be performed at the time of TME surgery depending on randomization and patient-specific risk of AL using the mAFOR score.

Experimental arm (arm A)

In the experimental arm (arm A) patients will undergo a two-step experimental intervention.

First, a decision to form a defunctioning stoma or not will be made based on personalized AL risk using the mAFOR score. This score has seven categories from 0 to 6 from a cumulative risk score based on gender, body mass index, smoking status, diabetes, size of tumour and preoperative RT. Patients with an mAFOR score of 0 or 1 (risk of AL less than 10%) will not undergo stoma formation (arm A₀₋₁). Patients with an mAFOR score between 2 and 6 (risk of AL exceeding 20%) will undergo stoma formation (arm A₂₋₆).

Secondly, patients in arm A₂₋₆ will undergo early closure of stoma (between POD 8 and 12) based on the following criteria being met:

- absence of postoperative fever (>38°C)
- CRP less than 115 mg/l (+/- 10 mg/l) on POD 2, decreasing on POD 4
- no evidence of AL on CT abdomen and pelvis with retrograde contrast enema performed on POD 7

If one of these criteria is not met, patients will remain with the defunctioning ileostomy as standard for 2–3 months. Furthermore, patients will automatically remain with a defunctioning stoma for 2–3 months if one of the following intra-operative events occurs:

**TABLE 2** Inclusion and exclusion criteria for GRECCAR 17 trial

Inclusion criteria
• ≥18 years old • Histologically confirmed rectal adenocarcinoma • Rectal tumour <12 cm from the anal margin (on rectal examination or MRI) • Stapled anastomosis performed <7 cm from the anal margin • Minimally invasive TME performed (laparoscopic, robotic, TaTME) • No evidence of metastasis (M0) • Both neoadjuvant and non-neoadjuvant receiving patients will be considered • Normal haematological levels as follows: haemoglobin ≥10.5 g/dl, leucocytes >4000/mm³, platelets >100 000/mm³ • Appropriate renal function: serum creatinine <15 mg/l • Appropriate liver function: AST/ALT <100 IU/l • Informed consent can be provided
Exclusion criteria
• Handsewn anastomosis • Open TME performed • Irradiated pelvis for cancers other than rectum, e.g. prostate or gynaecological, within the past 5 years • Colostomy in situ • Perforated tumour and pelvic sepsis preoperatively • Acute colitis or bowel obstruction • Patients operated on in emergency • Beyond TME resection or pelvic exenteration • Biochemical malnutrition: albumin <34 g/l, pre-Alb <0.14 g/l • History of the following comorbidities: ischaemia heart disease, congestive cardiac failure, immunosuppression and/or active corticosteroid therapy, severe pulmonary disease, chronic renal failure • Pregnancy and active breast feeding • Incapable of providing informed consent Where incapable of give their consent; • All conditions including psychological, geographical and social that could hinder adherence to the trial protocol

Abbreviations: AST/ALT, ratio of aspartate transaminase and alanine transaminase; pre-Alb, prealbumin; TaTME, transanal total mesorectal excision; TME, total mesorectal excision.

- >2 staple firings required
- intra-operative blood loss >250 ml
- intra-operative faecal contamination
- incomplete anastomotic doughnuts
- positive air leak test

Control arm (arm B)

In the control arm (arm B) a defunctioning ileostomy will be formed for all patients and reversal performed at 2–3 months postoperatively in keeping with French national guidelines.

Surgery

All patients will undergo minimally invasive TME, that is, laparoscopic, robotic or transanal TME, for rectal cancer with colorectal

anastomosis performed at <7 cm from the anal margin. The operative approach will be at the discretion of the operating surgeon. All oncological principles of TME will be observed.

Quality assurance

A research associate will be appointed by the sponsor to perform investigating site visits on a regular basis during the set-up and conduct of the trial (number of visits depending on rate of inclusions) with a final visit at study completion. During each visit the following elements will be examined:

- informed consent procedures and documentation
- protocol adherence
- quality of data collection (completeness, accuracy, missing data, consistency with source data)

All visits will be completed by a written report submitted to the trial monitoring committee.

Outcome assessment

The primary outcome is the overall quality of life 12 months following surgery. The European Organization for Research and Treatment of Cancer quality of life questionnaire QLQ-C30 will be completed at inclusion and postoperatively at 1, 4, 8 and 12 months for the primary outcome.

The following secondary outcomes will also be assessed and reported:

- anastomotic leak rate (clinical and radiological) at 1 and 4 months postoperatively
- quality of life outcomes, reported as QLQ-C30 (overall score and categories) at 1, 4, 8 and 12 months
- quality of life outcomes, reported as QLQ-CR29 (overall score and categories) at 1, 4, 8 and 12 months
- bowel function (low anterior resection syndrome and Wexner) at 1, 4, 8 and 12 months
- sexual function (International Index of Erectile Function or Female Sexual Function Index) at 1, 4, 8 and 12 months
- urinary function (Urinary Symptom Profile) at 1, 4, 8 and 12 months
- return to work time (days)

Assessment schedule and follow-up

All patients will be followed for a 12-month period postoperatively as summarized in Table 3. Patients will attend face-to-face visits at inclusion and 1, 4, 8 and 12 months postoperatively with clinical, quality of life and functional assessment at each attendance.



TABLE 3 Schedule of study events

	Pre-inclusion	Inclusion/randomization (D-30 to D-1)	Surgery (TME) D0	During hospitalization		Follow-up (± 15 days)			
				Postoperative arm A ₀₋₁	Postoperative arm A ₂₋₆	M1 review	M4 review	M8 review	M12 review
Patient information	x								
Signed consent	x								
Confirmation of eligibility		x							
Clinical examination ^a		x				x	x	x	x
Biochemical tests ^b	x					x	x	x	x
MRI	x								
Postoperative evaluation				Daily					
Clinical examination and temperature				POD 2-4					
CRP									
CT AP with retrograde contrast									
Quality of life assessment QLQ-C30 and QLQ-CR29		x				x	x	x	x
LARS		x				x ^c	x	x	x
Wexner		x				x ^c	x	x	x
IIIEF-5/FSFI		x				x	x	x	x
USP		x				x	x	x	x
EQ-5D-5L		x				x	x	x	x
Clavien-Dindo morbidity/mortality						x	x		
Professional activity questionnaire		x				x	x	x	x
Toxicity/SAE assessment	x	x	x	x	x	x	x	x	x

Abbreviations: AP, abdominal and pelvic; CEA, carcinoembryonic antigen; CRP, C-reactive protein; D, day; ECOG, Eastern Cooperative Oncology Group; FSFI, Female Sexual Function Index; IIIEF, International Index of Erectile Function; LARS, low anterior resection syndrome; M, month; SAE, serious adverse event; USP, Urinary Symptom Profile.

^aClinical examination: digital rectal examination (or, if not possible, MRI), review comorbidities, medications, past medical and surgical history, weight, ECOG score, preoperative therapy and tumour size and location.

^bBiochemical tests: full blood count, renal profile, liver profile, albumin, tumour markers (CEA and CA19-9).

^cLARS and Wexner score assessment not relevant to arm B at M1 visit as stoma still in situ.

Sample size calculation

Based on literature recommendations, an effect size of 0.5 is a clinically relevant difference threshold for the QLQ-C30 global quality of life score. Assuming a 20-point variation, this would correspond to a 10-point difference between the two groups. With a type I error of 5% and a power of 90%, the number of patients needed is 90 patients per arm, inflated to 100 patients per arm to take into account a 10% loss to follow-up, for a total of 200 patients.

Statistical analysis

The study data will be analysed by a biostatistician of the Clinical Epidemiology Unit. Analyses will be performed according to the intention-to-treat principle, whereby all randomized patients will be analysed in the treatment group to which they were originally randomized, and all of their data will be used, regardless of changes during the follow-up period.

Quantitative variables will be compared using a Student's test, a Student's test for unequal variances or a non-parametric test of Wilcoxon as a function of the terms applications of these tests. A linear regression model will be used to adjust for predictive factors and confounding. The hypothesis model (normality and linearity of the association for the quantitative factors) will be systematically verified. A transformation of the criteria may be granted in the event of deviation from the assumptions of the models.

Qualitative variables will be compared by a chi-squared test, a corrected chi-squared test or a Fisher exact test according to the distribution of data under the hypothesis of independence. Logistic regression models will be used for prognostic factors. The hypothesis model (normality and linearity of the association for the quantitative factors) will be systematically verified. Linear mixed models will be used to assess variable evolution longitudinally.

All statistical tests will be performed with a risk of type I error of 5%. For secondary analyses (except economic analyses), the multiplicity of statistical tests will be taken into account by controlling the false discovery rate (Benjamini and Hochberg). For each variable, the number of missing data will be described. The reason for being missing will be documented as much as possible in order to interpret the results. Missing data for the primary outcome will be considered as a failure of the strategy. Sensitivity analyses for missing data will also be performed (maximum bias analysis, analysis of complete cases, on a case-by-case basis after discussion with the scientific council [blinding the randomization arm and evolution], multiple imputation analysis etc.).

Economic analysis

A cost-effectiveness analysis will be performed to assess the health economic impact of a tailored approach to defunctioning

stoma formation. This will be by estimating the incremental cost per quality-adjusted life-year gained between arm A and arm B at 12 months post intervention, in the perspective of the French Health Care System. Direct hospital and ambulatory costs will be gathered by matching the GRECCAR 17 database with the French National Health Insurance Database, a claim database encompassing 98.8% of the French population [36].

As part of this system EQ-5D-5L will also be measured at inclusion and 1, 4, 8 and 12 months postoperatively. The GRECCAR 17 trial has been registered with the EuroQoL Group who administer the usage rights.

Trial management

The GRECCAR 17 trial will be led by the principal investigator QD. A trial management group comprising the principal investigator, trial assistants, coordinators and co-applicants will be established to implement and manage the clinical and practical running of the trial. Patient randomization and data management will be performed by a biostatistician from the Methodology and Data Management Centre before study commencement.

An independent data monitoring and ethics committee will be established to monitor safety, data and ethical considerations relating to the trial and provide independent recommendations. The data monitoring and ethics committee will convene during trial set-up and agree data to be presented and monitored at regular interval meetings and at minimum annually during both recruitment and follow-up to completion of the trial.

Serious adverse events

All serious adverse events (SAEs) will be immediately reported by the principal investigator to the safety and vigilance unit of the sponsor. The safety and vigilance unit will then report any suspected or unexpected (suspected unexpected serious adverse reaction, SUSAR) event to national authorities. The investigator will follow the participant with SAE or SUSAR until its resolution, stabilization to a level deemed as medically acceptable or return to previous state even if the participant has stopped the research. All SUSARs will be reported within 15 days of the index event. The safety and vigilance committee will provide the first safety report to the French Agency of Drug Safety (Agence Nationale de Sécurité des Médicaments et des Produits de Santé) and the French ethics committee within 60 days of first patient inclusion and a subsequent annual summary of all SUSARs and SAEs relating to the experimental arm.

Ethics and regulatory considerations

The GRECCAR 17 trial has received approval from the French ethics committee and authorization from the Agence Nationale de Sécurité

des Médicaments et des Produits de Santé. It will be conducted in accordance with standard principles of good clinical practice for conducting clinical trials and all recommendations from the World Medical Association Declaration of Helsinki and the European Union Regulation 2016/679. The trial will be sponsored by Bordeaux University Hospital and appropriate public liability insurance policy provisions will be made in accordance with the French Public Health Code.

Dissemination

The results of this trial will be presented at national and international scientific meetings and formal publication will be sought in peer-reviewed journals.

DISCUSSION

The GRECCAR 17 trial will be the first definitive phase III trial to investigate a patient-tailored approach to defunctioning ileostomy following TME compared to a systematic use as has been the previous standard of care. Furthermore, using patient quality of life as a primary outcome and performing extensive assessment of functional outcome up to 12 months postoperatively is a progressive approach to ensuring patient-centred rectal cancer research. Combining two strategies of patient-tailored stoma management (first regarding the decision to form a stoma and second regarding the timing of closure) also facilitates a robust evaluation of the clinical role for a patient-tailored stoma formation strategy.

While the previous standard of care following TME with colorectal anastomosis <7 cm from the anal margin was to systematically fashion a defunctioning ileostomy it has become evident that defunctioning ileostomy is not without risk and can be associated with significant morbidity and long-term complications [22–30]. Furthermore, return of normal bowel function following reversal appears to be negatively impacted with increasing duration of stoma use. In this trial all stoma-related complications will be rigorously recorded and classified according to the Clavien–Dindo classification. Through our initial feasibility study, we have demonstrated that, utilizing the mAFOR score, patients can be safely risk stratified to stoma use or not and combining mAFOR score, serial postoperative CRP and CT with retrograde enema can safely identify patients who benefit from early stoma closure (in the press). The GRECCAR 17 trial will allow us to assess this patient-tailored approach definitively in an RCT study design and comprehensively to assess the impact of defunctioning ileostomy and the patient-tailored approach on patient quality of life and functional outcome including bowel, urinary and sexual function and return to work.

Patient-reported outcome measures, quality of life and functional outcomes require greater focus in rectal cancer research [37]. To date, few studies have used a quality of life measure as a primary outcome in rectal cancer research especially with a composite score.

The GRECCAR 17 trial will represent a significant step towards this paradigm shift as the primary outcome will be based on QLQ-C30, a global quality of life score used and validated in oncology research, but also including a comprehensive assessment of quality of life, functional outcomes (including urinary, sexual and bowel function) and impact on professional function as secondary outcomes [38]. All outcomes will continue to be assessed for up to 12 months postoperatively. Assessment of QLQ-C30 over time will also be informative and considering the reliability and validation of the QLQ-C30 it was deemed the most suitable tool for primary outcome reporting. Overall score and individual domains will be reported. The colorectal cancer specific QLQ-CR29 quality of life reporting tool will also be used as a secondary outcome.

Similar to quality of life, the economic impact of ileostomy use following TME for rectal cancer is understudied. Whilst using a defunctioning ileostomy following TME for rectal cancer can reduce the clinical significance of AL when it occurs, the requirement for stoma appliances and further operative procedures for stoma reversal and in some cases to treat complications can have a significant health economic impact. Two studies have reported significantly less healthcare and hospital costs of over €5000 in patients without a stoma following low anterior resection for rectal cancer [33, 39].

There are some key challenges to consider in the delivery of the GRECCAR 17 trial. First, using quality of life as a primary outcome is often criticized as it is a subjective measure. However, we believe that the subjective experience of the patient is what is important and using both the QLQ-C30 and QLQ-CR29 measures will allow comparison and standardization. To complete early stoma reversal, theatre access on potential non-assigned elective surgery days will also be required within the POD 8–12 window. Finally, a clear consent process has been planned but some patients who have a low mAFOR score that could avoid a stoma may have difficulty accepting randomization to the control arm where stoma formation will be performed systematically. This potential effect has been highlighted by the research team to require careful monitoring.

In summary, the GRECCAR 17 trial will definitively investigate the quality of life impact of a patient-tailored approach to defunctioning ileostomy following TME for rectal cancer. Patient risk stratification based on the risk of AL using the mAFOR score will validate this approach to tailored versus systematic ileostomy use. Furthermore, GRECCAR 17 will provide a comprehensive report of quality of life, functional outcomes and health economic analysis of a tailored approach to stoma formation following TME. This is important as we are in an era where the critical importance of patient-reported outcomes and functionality in survivorship are better recognized.

FUNDING INFORMATION

French Ministry of Health.

CONFLICT OF INTEREST

The authors declare no conflict of interest relating to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The GRECCAR 17 trial has received approval from the French ethics committee and will be conducted in accordance with the principles of good clinical practice in trial conduct and the recommendations of the World Medical Association Declaration of Helsinki and the European Union Regulation 2016/679.

TRIAL REGISTRATION

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