BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

"EMPACOL PROJECT": THE ROLE OF EMPATHY IN THE OUTCOMES OF COLORECTAL CANCER. PROTOCOL OF A POPULATION BASED-STUDY IN TWO FRENCH AREAS

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066559
Article Type:	Protocol
Date Submitted by the Author:	13-Jul-2022
Complete List of Authors:	Mulliri, Andrea; CHU Caen, Lelorain, Sophie; University of Lille, Psychology, Cancer care Bouvier, Véronique; Centre Hospitalier Universitaire de Caen Bara, Simona; CH du Cotentin Gardy, Josephine; Centre Francois Baclesse Centre de Lutte Contre le Cancer Grynberg, Delphine; Université de Lille MORELLO, Rémy; CHU Caen, Unité de biostatistique et recherche clinique Alves, Arnaud; CHU Caen Dejardin , Olivier; Centre Hospitalier Universitaire de Caen, INSERM U1086 Anticipe
Keywords:	SURGERY, Gastrointestinal tumours < GASTROENTEROLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

"EMPACOL PROJECT": THE ROLE OF EMPATHY IN THE OUTCOMES OF COLORECTAL CANCER. PROTOCOL OF A POPULATION BASED-STUDY IN TWO FRENCH AREAS

Andrea Mulliri[1,2], Sophie Lelorain[3], Veronique Bouvier [2,4,7], Simona Bara[5], Josephine Gardy[2], Delphine Grynberg[3], Remy Morello[6,7], Arnaud Alves [1,2,7], Olivier Dejardin [2,7]

Correspondence to:
Andrea Mulliri
dr.andreamulliri@gmail.com

Author affiliations:
[1]Department of digestive surgery, University Hospital of Caen, Caen, France.
[2] ANTICIPE" U1086 INSERM-University of Caen Normandy, Team « Ligue contre le Cancer », Centre François Baclesse, Caen, France.
[3] Univ. Lille, CNRS, UMR 9193 - SCALab - Sciences Cognitives et Sciences Affectives, 59000, Lille, France.
[4] Digestive Tumors Registry of Calvados, University Hospital of Caen, U1086 INSERM UCN-ANTICIPE, French Network of Cancer Registries (FRANCIM), Caen, France.
[5] Registre des Cancers de la Manche, Cherbourg-Octeville, France.
[6] Department of biostatistics and clinical research, University Hospital of Caen, Caen cedex, France.
[7] Department of research, University Hospital of Caen, Normandy, France

ABSTRACT

Introduction

The aim of our project (EMPACOL) will be to investigate the patient-healthcare personnel (HCP) relationship with patients diagnosed with non-metastatic colorectal cancer and how HCPs' empathy perceived by patients may influence the curative treatment of their diagnosis. This investigation will take into consideration the known clinical factors that are well described in the literature as well as the non-clinical factors.

Methods and Analysis

EMPACOL will be a descriptive longitudinal study that documents multicenter perspectives. Over two years involving two French areas covered by a cancer register, eight cancer treatment centers will be included where patients with non-metastatic CRC, uncomplicated at diagnosis are being treated. Based on the curative strategy, patients will be divided into three groups: Group 1 (surgery alone), Group 2 (surgery and adjuvant chemotherapy), and Group 3 (neoadjuvant therapy, surgery, and adjuvant chemotherapy).

The relationship between HCP's empathy perceived by the patient at the time of announcement and the end of the strategy, the reported quality of life (QoL) at one year following treatment, and the oncological outcomes after five years will be investigated. HCP's empathy and QoL will be evaluated respectively with the CARE and QoL C-30 questionnaire. A relationship

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

between HCP's empathy and early outcomes, particularly in terms of digestive and genitourinary sequelae, will also be studied for each treatment group. Post-treatment complications will be assessed using the Clavien Dindo classification.

Each assessment of HCP's empathy will be associated with an estimation of the patient's emotional sphere using the HADS questionnaire.

Ethics and Dissemination

The Institutional Review Board of the University Hospital of Caen and the ethics committee (CPP Nord Ouest I, June 2022) approved the study.

Trial registration number: NCT05447611

EMPACOL project

Strengths

- the multicenter and prospective design of the study and the longitudinal aspect of the project
- the multidisciplinary nature of the research group made it possible to address functional sequelae, socio-territorial inequalities, and empathy, and to assess the impact of clinical and non-clinical factors in CRC
- supervision of the cancer registry to ensure that the results are representative

Limitations

- the lack of a CARE score threshold in the literature
- temporal and spatial heterogeneity between clinical information and questionnaire completion

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BACKGROUND

Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) remains a public health problem. There were an estimated 43,336 new cases of CRC in France in 2018. This makes it, among solid tumors, the third most common cancer in men and the second most common in women. With 17,117 deaths in 2018, CRC is the second-leading cause of cancer death in men and the third-leading cause of death in women. The prognosis of CRC has improved significantly over the past 20 years [1, 2]. For patients with colon cancer (CC) a five-year survival rate is ranged from 92% for stage I to 11% for stage IV, respectively. The multidisciplinary strategy for rectal cancer (RC) has been shown to reduce the five-year local recurrence rate to less than 10%, and increase the five-year overall survival (OS) rate beyond 50% [3].

CRC Management

Although the term "colorectal cancer" is commonly used, both multimodal treatment and functional sequelae are not the same for colon and rectal cancer [4]. For forms that are neither metastatic nor locally complicated (non-hemorrhagic, without occlusion or perforation) at the time of diagnosis, surgical oncologic resection (colectomy or proctectomy) represents the cornerstone of treatment with curative intent [5]. As suggested by recent French guidelines [6], surgery is preceded by neoadjuvant treatment for locally advanced subperitoneal rectal cancer (RC). Adjuvant chemotherapy (ADJ CT) is recommended in the case of lymph node involvement (stage III) or vascular/lymphatic invasion, peri-nerve, or tumor budding. The short-term outcome of surgical resection is generally reported by mortality rates and morbidity using the Dindo-Classification Score assessed on the 90th postoperative day [7]. Since the 2000s, the three-month mortality of CRC patients, regardless of surgical treatment, has decreased significantly from 15.8% to 11.3% [8].

Both overall and recurrence-free survival are usually the parameters for assessing long-term oncological outcomes. Although OS has increased significantly over time in all European

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

regions [9], the five-year OS rate for both CC and RC depends on lymph node status (N) and cancer stage (T) [10].

Due to the significant improvement in prognosis, the functional dimensions of CRC treatment have now become inseparable from carcinological imperatives [11]. Historically, functional sequelae have long been considered inherent to the carcinological nature of the surgical resection and, hardly avoidable. While the prevalence and predictive factors are different depending on colonic or rectal location [12]. Functional sequelae (i.e., digestive and/or genitourinary sequelae) may impair patients' QoL significantly.

Quality of Life

While QoL remains a priority among CRC treatment outcomes, as outlined in Axis 2 of the PLAN CANCER FRANCE, a 10-year strategy for 2021-2030, little is known regarding the evolution of QoL over time in patients operated on for CRC [13]. Most QoL scores drop significantly in the early postoperative period. Surgery, especially total mesorectal excision in RC is known to reduce QoL among patients significantly [12]. Of all digestive cancer removals, proctectomy for RC carries the greatest risk of functional sequelae and impaired QoL [12]

Among the functional sequelae observed, the definitive stoma in case of abdominoperineal excision and the digestive sequelae in sphincter conservation represent the two main risk factors of alterations in QoL.

Globally, CC patients have less disabling outcomes compared to patients who have undergone RC surgery [4]. In the case of ADJ CT, many negative side effects are reported. Some toxicities persist after discontinuation of treatment, which may result in changes in patients' QoL.

Role of Empathy in Care

According to the definition by Collins, empathy is the ability to share another person's feelings and emotions as if they were your own. In the humanities sciences, the precise definition of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

empathy is the subject of ongoing academic debate. Empathy is often considered one-dimensional, but recent work has demonstrated that a multidimensional view of the concept is also conceivable in oncology [14,15]. Empathy is considered essential for the formation, development, and continuation of the therapeutic patient-healthcare professional relationship.

In a clinical setting, empathy involves an ability to:

-understand the patient's situation, perspective, and feelings

-communicate this understanding and verify its accuracy

-act on this understanding with the patient in a helpful way (joint planning of an optimal therapeutic strategy).

Empathy is associated with decreased distress and anxiety among patients [16] and increased treatment adherence [17].

Other benefits of empathy include enhanced emotional management of the burden of illness, emotional acceptance, reduced anxiety, and satisfaction with care, which persists after the announcement of diagnosis [18,19,20]. Perceived empathy is largely explained by patient-driven and clinical variables [21]. Unmet patient needs are strongly and positively associated with low medical staff empathy. As such, the quality of the patient-medical staff relationship is positively associated with practitioner empathy [16].

A systematic literature review suggests a positive association between HCPs' empathy and a variety of positive patient outcomes, including increased satisfaction with care and improved QoL [16].

The evaluation of empathy must be done at several key moments of the care journey to measure the trajectories of empathy perceived and the link between these trajectories and the outcomes of interest. For example, patients with CRC who require first-line CT present more major concerns at the time of their initial CT education sessions compared to the mean index/average concerns of patients with other tumor forms [22].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Only one study has revealed the link between empathy and survival in oncology, however, it was done retrospectively (historical cohort) and they found discordant results depending on when empathy was requested [23].

To our knowledge, no prospective study has specifically examined the relationship between patient-perceived empathy at each stage of treatment and the consequent CRC outcomes.

Hypothesis and Objectives of the Investigations

The main objective of the EMPACOL project is to investigate, in non-metastatic CRC patients, a possible correlation between perceived HCP empathy and survival (OS and DFS).

The secondary objective is to evaluate the relationship between perceived HCP empathy and QoL and morbidity and mortality in patients treated for curative non-metastatic CRC.

We expect to find a positive correlation between perceived HCP empathy (the patient's perception of the curative treatment received) and a reduction in morbidity/mortality and an improvement in both functional outcome and consequent QoL after one year of the performed treatment.

We also aim to verify if a positive correlation exists between a high score and an improvement in survival (OS, DFS) after five years (Figure 1).

METHODS

EMPACOL Project Design

EMPACOL is a descriptive longitudinal study that will aim to investigate multicenter perspectives involving two French areas covered by a cancer registry. The project has been approved by the CPP. All investigators will conduct this study by the Declaration of Helsinki.

Patients with non-metastatic CRC will be included from eight surgical units in France (see the list of participating centers in the Acknowledgments section) involved in the management of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CRC, with the aim of conducting and publishing multicenter clinical trials on the theme of perceived HCP empathy, QoL, and survival.

To anticipate and respond to the questions and issues that will be encountered in the EMPACOL project and future studies, we have planned to design a prospective multicenter pilot study (Figure 2) which will be integrated into the EMPACOL project.

Patients will be included prospectively over a period of six months. The pilot study aims to find a link between the circuit of the questionnaire adopted by the center and the rate of response to the questionnaires. Factors that may influence the response rate will also be assessed.

The proposed questionnaire circuit foresees the patients within Groups 1 and 2 and evaluates the perceived HCP empathy after surgical consultation. For the patients within Group 3, perceived HCP's empathy will be evaluated once the patient meets their medical and paramedical team (oncologists, radiotherapists, and surgeons), and the therapeutic sequence has been validated during a multidisciplinary consultation (MDC). Subsequent measurement of the perceived HCP's empathy will be carried out at the end of the therapeutic sequence. Each assessment of perceived HCP's empathy will be associated with an assessment of the patient's state of anxiety and depression (according to the HADS questionnaire) (Figure 3).

We expect participating centers to indicate when the proposed circuit questionnaire will pose difficulties in terms of filling, delivery, or recovery, to optimize and streamline the following stages of the EMPACOL project. We suggest to the participating centers that they send and collect communications and the questionnaires with patients by postal service.

QoL will be evaluated for the three therapeutic groups at the time of the announcement of the strategy simultaneously with perceived HCP empathy. The patients' QoL will be reassessed on the 90th postoperative day for Group 1 and at the end of the ADJ CT for Groups 2 and 3. Regardless of the therapeutic group, QoL will be reassessed at six months and one year after the end of treatment (Figure 3). We will aim to find a link between perceived HCP's empathy and QoL (the primary objective) and we will also study the link with morbidity and mortality of the treatment received (the secondary objective). Morbidity and mortality will be evaluated

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

at the end of the therapeutic strategy. The most severe complication will be considered in the analyses (Figure 2)

To assess the impact of perceived HCP's empathy on oncological results, a link will be sought between overall survival at five years (the primary objective) and the appearance of local recurrence or metastatic pathology (the secondary objective).

The disease will be considered metachronous in the event of a delay of appearance at six months about the diagnosis. (Figure 2)

Inclusion Criteria

We included patients aged 18 to 80 years, who were French-speaking, affiliated with a social security system, had received informed information, and not having expressed an unfavorable opinion about participating in the strategy. Carriers of non-metastatic and uncomplicated CRC (without occlusion/ perforation/bleeding), require elective therapeutic management. The included patients have a cognitive state capable of understanding and completing the questionnaires (autonomous completion).

Exclusion Criteria

We excluded patients who were minors or older than 80 years, those who resided in a department outside Calvados or Manche, those who presented a CRC other than adenocarcinoma and all metastatic forms or requiring emergency surgery (perforation, hemorrhage, occlusion), exclusive of endoscopic treatment, or a missed-CRC discovered after surgery for non-oncological indications.

We also excluded patients with other neoplastic diseases under treatment and/or evolving, as well as patients with a history of inflammatory bowel disease (Crohn's disease, ulcerative colitis) and/or hereditary disease predisposing to CRC (Lynch syndrome, familial polyposis) or with severe cognitive impairment preventing proper comprehension of the questionnaires. Pregnant women will also be excluded.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Endpoints and Measures

Empathy

Patient-perceived empathy was assessed using the Consultation and Relational Empathy (CARE) questionnaire that has been validated in cancer care. This is a self-reported ten-point questionnaire with a Likert-type five-point scale ranging from "poor" to "excellent". It has excellent psychometric properties with $\alpha = 0.92$. High scores indicate higher perception of the health care personnel's empathy.

The three distinct empathic processes were also assessed with the CARE measure. “Relationship” was assessed with items 1-3, “emotional process” with items 4-6, and “cognitive process” with items 7-10.

Quality of Life

QoL will be evaluated using the EORTC-QLQ-C30 questionnaire. The EORTC-QLQ-C30 is equivalent to other tools, such as the GIGLI, in terms of emotional function, but superior in terms of social function [24]. The use of an additional tool is recommended for the assessment of depression in CRC patients [25].

Patient Anxiety and Depression

This parameter was evaluated with the HADS [26]. The HADS scale assesses both anxiety and depression, which commonly coexist.

Morbidity and Mortality

The severity of medical and surgical complications was assessed using the Clavien-Dindo grading system [7]. Grades I and II complications involve only pharmacological treatment, while grades III, IV, and V require surgical, endoscopic, or radiological treatment. Complications below grade III were considered “minor complications” while complications above and including grade III were considered “major complications”, as reported in the literature. For the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

three groups, postoperative morbidity and mortality will be assessed at 90 postoperative days (C/D90). C/D90 will be associated with the morbidity and mortality of the other therapeutic stages, post adjuvant treatment for Group 2 (C/DADJ) and post neoadjuvant treatment (C/DNEOADJ) for Group 3, also with C/DADJ.

Survival and Representativeness of the Data Collected

All patients diagnosed with CRC during the inclusion period were included in two specialized digestive cancer registries of North-West France, and were members of the French network of cancer registries (FRANCIM), the department of Calvados, and Manche. The resident population of these well-defined administrative areas was 1,601,928 inhabitants in 2016. Both digestive cancer registries included in the present study collected exhaustive information on treatments and stages in the framework of a high-resolution study. These registries have worked together for many years and use identical standardized data collection, recording, and validation procedures. Multiple information sources ensure an exhaustive collection of study variables. The databases are declared to the National Commission on Information Technology and Civil Liberties (CNIL). The quality of the data collected is evaluated every four years by the Institut National de la Santé et de la Recherche Médicale (INSERM), “Santé Publique France”, and theInstitut National du Cancer (INCa).

Data Collection

The medical information included gender, age (<60 years, 60–69 years, 70–75 years), obesity score (BMI > 30), active smoking and alcohol use report, the ASA physical status classification system (I-II versus III-IV), anxious and depressive states (HADS score) of the patient and presentation at the multidisciplinary consultation, histology and tumor differentiation (grades I, II, and III), surgical approach (laparotomy and/or laparoscopy or robotic), as well as neoadjuvant or adjuvant treatments (type and number of sessions), and the site of the primary tumor (colon vs rectum). The forms located at the rectosigmoid junction were included in the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

colonic localizations. Socio-demographic information such as education level and marital status were used as extracted from the CRF.

Socioeconomic status was defined using the European Deprivation Index (EDI), which is an ecological and composite indicator included in the census of the European Union's statistics on income and living conditions. For all cases, patient addresses were geolocalized using the geographic information system (ArcGIS 10.2) and assigned to a "Ilots Regroupés pour L'Information Statistique" (IRIS), a geographic area defined by the "Institut National de la Statistique et des Études Économiques" (INSEE). IRIS is the smallest geographical unit in France, for which census data are available.

STATISTICAL ANALYSIS

Quantitative variables will be expressed as the mean ± SD, and qualitative variables will be expressed as the number of patients and percentages. Regardless of the therapeutic group, the experimental design of the study allows for several measurements to be performed on the same individual during his or her oncological care and follow-up. Comparisons between the mean scores of the three treatment groups will be made using an analysis of variance (ANOVA) or a Kruskal-Wallis test, depending on whether the data follow the hypothesis of tested homoscedasticity. Post hoc comparisons will be performed using the Bonferroni Correction or the Nemenyi Test.

The sensitivity and specificity of the CARE score in predicting the impact on QoL will be assessed by receiver operating characteristic curves for the score versus groups reporting no/minor or definite/major impact on QoL.

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

The inclusion of data indicating the impact of CARE on QoL will be based on a univariate approach and then a multivariate approach using ad hoc models depending on the nature of the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

dependent variable (binary or multi-nominal logistic regression or linear regression depending on whether the Quality of Life score is considered qualitative or quantitative). Only variables with p<or = 0.20 in the univariate analysis of will be included in the multivariate model. This approach will allow the identification of risk factors related to the deterioration of QoL and the assessment of their impact. All tests will be two-tailed with a significance level (p) equal to 0.05.

We will use the Kaplan-Meier method to obtain survival curves and a Cox model to assess the impact of CARE score on survival in the three different groups. Hazard ratios (HRs) were calculated, using semi-proportional Cox hazard models, to assess the effect of the CARE score on survival in patients with nonmetastatic, uncomplicated CRC. The proportional hazard hypothesis will be tested (Schoenfeld's residuals). Variables whose threshold p-value was ≤0.20 in univariate analysis (M0) will be included in the multivariate model (M1). The variable of interest (CARE score) is going to be forced into all models.

All statistical analyses will be performed using StataSE14 (StataCorp LLC, College Station, Texas, USA).

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

Eight colorectal cancer centers, including both teaching hospitals and cancer centers, agreed to include 50 to 100 patients who received curative treatment between XXX and XXX (see Acknowledgments for list of participating centers). The availability of patients for inclusion in the study at each center has been demonstrated in published studies. We chose to include patients who had undergone curative treatment over two years for two reasons: the first being

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

physiological, to allow their bowel function to become stable. The second is oncological, to detect local recurrence and/or distant metastases. Consistent with the recent literature, we considered differentiating the study population into two groups: those with high perceived empathy (maximum CARE score) and those without.

We calculated with BiostaTGV that approximately 90 patients in each group, thus 180 in total, would be needed to show clinically significant improvement in quality of life or reduction in morbidity with high CARE score (power β 80% and risk α 0.05 bilaterally).

From the two cancer registries, we know that over the 2-year inclusion period, the number of nonmetastatic colorectal cancers is approximately 480 cases.

Assuming that the lost-to-follow-up rate is approximately 50%, we estimate that we will be able to include 250 patients.

DISCUSSION

The prognosis of CRC has improved significantly over the past 20 years [1,2]. Oncologic principles [27], the development of minimally invasive techniques [28], and advances in diagnostic accuracy [29] are strongly linked to these outcomes and are well described in the recent literature. However, many surviving patients experienced functional sequelae (i.e., digestive and/or genitourinary sequelae), that significantly impaired their QoL. Both prevalence and predictive factors are different depending on colonic or rectal location [12].

Functional disorders occur frequently following surgery for CC. The incontinence of liquid and solid stool is 24.1% and 6.9%, respectively. The most common symptoms associated with constipation are incomplete and difficult evacuation in about one-third of cases [4]. Major Low Anterior Resection Syndrome (LARS) was present in 21.1% [4]. No difference is reported in the prevalence of symptoms according to the type of colectomy [4,12]. In their systematic review and meta-analysis, Verkuijl et al. included 8,418 partial colectomies (4,207 right hemicolectomies and 4,211 left hemicolectomies/sigmoid colon resection, respectively), and 161 subtotal/total

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

colectomies and concluded that bowel function problems following colon cancer surgery are common, tend to not improve over time, and are not dependent on the type of surgery.

For RC, low rectal resections [30] and neoadjuvant radiotherapy [31] are known to severely impair bowel function. Up to 80% with RC undergo sphincter-preserving surgery [32] , without impairing oncological prognosis [6,33]. Between 50 and 90% of these patients will experience a change in their bowel habits afterward [34,35]. Eid et al found that 65.2% of RC survivors had bowel dysfunction, including 41.3% with major low anterior resection syndrome and 80% with genitourinary dysfunction [12]. Indeed, in addition to the psychological burden related to the tumor pathology and the concern about the probability of recovery, it is important to consider the patient's experience of the functional results and its repercussions in terms of QoL, especially in the case of complications or poor functional results. One of the worst fears related to surgery is the creation of an ostomy.

Problems related to stoma care or impaired genitourinary or digestive function are likely to have an impact on the QOL of CRC patients [12].

Patients' perceived unmet rehabilitation needs during the course of their tumor pathology are associated with decreased QoL. Interventions to reduce cancer patients' perceived rehabilitation needs may improve QoL.

Among non-medical factors, other than socioeconomic and geographic inequalities, rural ostomy patients reported more care-related problems and lower QoL [36], the relationship between patient and caregiver influences the patient's experience throughout their care.

A 2012 review of the literature suggested links between oncology caregiver empathy and various positive patient outcomes such as improved QOL or increased satisfaction with care [16]. Assessment modalities for measuring empathy in medical settings are heterogeneous [16].

The associations between the severity of medical and surgical complications and the perception of surgeon empathy have been studied in esophageal and gastric cancer patients. When patients perceived high empathy, they were less likely to report major complications [15]. Of the three dimensions, "rapport-building" ($p = 0.019$) and "emotional process" ($p = 0.022$) were predictive

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of major complications. Physician empathy is essential before surgery and it is therefore important to consider the patient's experience.

By using the CARE tool, the EMPACOL Project will allow us to evaluate the role of empathy among medical and paramedical staff perceived by the patient throughout their care and its evolution over time, particularly in the case of complications related to treatment and its impact in terms of early and late results.

CONCLUSIONS

Health care providers need to be trained to establish a good relationship with patients, from the time of treatment announcement through the period of oncologic surveillance. Further research is needed to understand the mechanisms linking empathy to CRC management outcomes.

To this end, the pilot study will allow us to identify the best channel for distributing the questionnaire, study the clinical and non-clinical factors that may influence respondent and non-respondent rates, and look for a correlation with short-term outcomes in each therapeutic group.

The results of the pilot study will therefore help refine the methodological tools that will be used in the EMPACOL project, which aims to find a correlation between the CARE score and long-term outcomes (QoL and survival). The representativeness of the data collected and the results of the EMPACOL project will be studied through the supervision of the cancer registries that cover the two departments considered for patient inclusion.

Repeated measurements of perceived empathy, concerning the treatment received, in the same individual and a follow-up of their evolution over time, will make it possible to understand how to facilitate learning, encourage its practice in daily clinical attitudes and promote the development of empathy in the training of all actors in the caregiver-patient relationship. Obtaining and validating an empathy score, thanks to future studies, will allow a better appreciation of the role of all non-clinical factors in the results in the oncological environment and will also open the way to other typologies of cancer.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The originality of this project is to go beyond the impact of clinical factors on the outcomes of curative treatment of CRC. The multidisciplinary collaboration and cross-cutting competencies within our research group, functional sequelae, socio-territorial inequalities, and empathy, will allow us to better understand the impact of non-medical factors and the role of empathy in the curative treatment of CRC. The prospective and longitudinal nature of this project, thanks to the supervision of the cancer registry, will allow us to comment on the representativeness of the data collected and the results obtained.

Contributors Study conception and design**:** SL, AA, OD, AM. Intervention design: SL, VB, DG, JG, DG, AA, OD, SB and AM. Analysis of data will be done by AM, OD and RM. AA drafted the work, which was revised critically for intellectual content by SL. All authors gave final approval of this version to be published.

Competing interests None declared.

Funding The institutional promoter is the University Hospital of Caen Department of Clinical Research and Innovation

Data sharing statement This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Ethics and dissemination The institutional promoter is the University Hospital of Caen Department of Clinical Research and Innovation. Results of this study will be disseminated by publication through peer- reviewed professional and scientific journals. Participant data will be kept confidential and will not be shared with the public. If there are requests for data sharing for appropriate research purposes, this will be considered on an individual basis after trial completion and after the publication of the primary manuscripts.

ORCID ID Andrea Mulliri https://orcid.org/ **0000-0002-0333-8651**

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure 1 Schematic representation of the factors evaluated.

Figure 2 the EMPACOL design

Figure 3 Proposed questionnaire distribution circuit.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1. Ferlay, J. *et al.* Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* **49**, 1374–1403 (2013).
2. Siegel, R. L. *et al.* Colorectal cancer statistics, 2017. *CA Cancer J Clin* **67**, 177–193 (2017).
3. Cottet, V. *et al.* Incidence and Patterns of Late Recurrences in Rectal Cancer Patients. *Ann Surg Oncol* **22**, 520–527 (2015).
4. Verkuijl, S. J. *et al.* Functional outcomes of surgery for colon cancer: A systematic review and meta-analysis. *Eur J Surg Oncol* **47**, 960–969 (2021).
5. Labianca, R. *et al.* Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* **21 Suppl 5**, v70-77 (2010).
6. Lakkis, Z. *et al.* Management of rectal cancer: the 2016 French guidelines. *Colorectal Dis* **19**, 115–122 (2017).
7. Clavien, P. A. *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* **250**, 187–196 (2009).
8. Iversen, L. H., Ingeholm, P., Gögenur, I. & Laurberg, S. Major Reduction in 30-Day Mortality After Elective Colorectal Cancer Surgery: A Nationwide Population-Based Study in Denmark 2001–2011. *Ann Surg Oncol* **21**, 2267–2273 (2014).
9. Brenner, H. *et al.* Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: The EUROCARE study. *International Journal of Cancer* **131**, 1649–1658 (2012).
10. Gunderson, L. L., Jessup, J. M., Sargent, D. J., Greene, F. L. & Stewart, A. K. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol* **28**, 264–271 (2010).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11. Alves, A. [Recommendations for clinical practice. Therapeutic choices for rectal cancer. How can we reduce therapeutic sequelae and preserve quality of life?]. *Gastroenterol Clin Biol* **31 Spec No 1**, 1S52-62, 1S95-97 (2007).

12. Eid, Y. *et al.* Digestive and genitourinary sequelae in rectal cancer survivors and their impact on health-related quality of life: Outcome of a high-resolution population-based study. *Surgery* **166**, 327–335 (2019).

13. Schmidt, C. E., Bestmann, B., Kuchler, T., Longo, W. E. & Kremer, B. Impact of age on quality of life in patients with rectal cancer. *World J Surg* **29**, 190–197 (2005).

14. Gehenne, L. *et al.* Testing two competitive models of empathic communication in cancer care encounters: A factorial analysis of the CARE measure. *Eur J Cancer Care (Engl)* **29**, e13306 (2020).

15. Gehenne, L. *et al.* Associations between the severity of medical and surgical complications and perception of surgeon empathy in esophageal and gastric cancer patients. *Support Care Cancer* (2021) doi:10.1007/s00520-021-06257-y.

16. Lelorain, S., Brédart, A., Dolbeault, S. & Sultan, S. A systematic review of the associations between empathy measures and patient outcomes in cancer care. *Psychooncology* **21**, 1255–1264 (2012).

17. Street, R. L., Gordon, H. S., Ward, M. M., Krupat, E. & Kravitz, R. L. Patient participation in medical consultations: why some patients are more involved than others. *Med Care* **43**, 960–969 (2005).

18. Spencer, R., Nilsson, M., Wright, A., Pirl, W. & Prigerson, H. Anxiety disorders in advanced cancer patients: correlates and predictors of end-of-life outcomes. *Cancer* **116**, 1810–1819 (2010).

19. Mack, J. W. *et al.* Measuring therapeutic alliance between oncologists and patients with advanced cancer: The Human Connection Scale. *Cancer* **115**, 3302–3311 (2009).

20. Gattellari, M., Butow, P. N. & Tattersall, M. H. Sharing decisions in cancer care. *Soc Sci Med* **52**, 1865–1878 (2001).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

21. Lelorain, S. *et al.* How does a physician's accurate understanding of a cancer patient's unmet needs contribute to patient perception of physician empathy? *Patient Educ Couns* **98**, 734–741 (2015).

22. Oguchi, M. *et al.* Measuring the impact of nurse cue-response behaviour on cancer patients' emotional cues. *Patient Educ Couns* **82**, 163–168 (2011).

23. Lelorain, S., Cortot, A., Christophe, V., Pinçon, C. & Gidron, Y. Physician Empathy Interacts with Breaking Bad News in Predicting Lung Cancer and Pleural Mesothelioma Patient Survival: Timing May Be Crucial. *J Clin Med* **7**, E364 (2018).

24. Schwenk, W. *et al.* Comparison of EORTC quality of life core questionnaire (EORTC-QLQ-C30) and gastrointestinal quality of life index (GIQLI) in patients undergoing elective colorectal cancer resection. *Int J Colorectal Dis* **19**, 554–560 (2004).

25. Aminisani, N., Nikbakht, H., Asghari Jafarabadi, M. & Shamshirgaran, S. M. Depression, anxiety, and health related quality of life among colorectal cancer survivors. *J Gastrointest Oncol* **8**, 81–88 (2017).

26. Skarstein, J., Aass, N., Fosså, S. D., Skovlund, E. & Dahl, A. A. Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *J Psychosom Res* **49**, 27–34 (2000).

27. Rodríguez-Luna, M. R., Guarneros-Zárate, J. E. & Tueme-Izaguirre, J. Total Mesorectal Excision, an erroneous anatomical term for the gold standard in rectal cancer treatment. *Int J Surg* **23**, 97–100 (2015).

28. Crippa, J. *et al.* Robotic Surgery for Rectal Cancer Provides Advantageous Outcomes Over Laparoscopic Approach: Results from a Large Retrospective Cohort. *Ann Surg* **274**, e1218–e1222 (2021).

29. Zhu, G., Wu, Z., Lui, S., Hu, N. & Wu, M. Advances in Imaging Modalities and Contrast Agents for the Early Diagnosis of Colorectal Cancer. *J Biomed Nanotechnol* **17**, 558–581 (2021).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

30. Keane, C., Wells, C., O'Grady, G. & Bissett, I. P. Defining low anterior resection syndrome: a systematic review of the literature. *Colorectal Dis* **19**, 713–722 (2017).

31. Croese, A. D., Lonie, J. M., Trollope, A. F., Vangaveti, V. N. & Ho, Y.-H. A meta-analysis of the prevalence of Low Anterior Resection Syndrome and systematic review of risk factors. *Int J Surg* **56**, 234–241 (2018).

32. Chau, A. *et al.* Toward the end of abdominoperineal resection for rectal cancer? An 8-year experience in 189 consecutive patients with low rectal cancer. *Ann Surg* **260**, 801–805; discussion 805-806 (2014).

33. Rullier, E. *et al.* Sphincter-Saving Resection for All Rectal Carcinomas: The End of the 2-cm Distal Rule. *Annals of Surgery* **241**, 465–469 (2005).

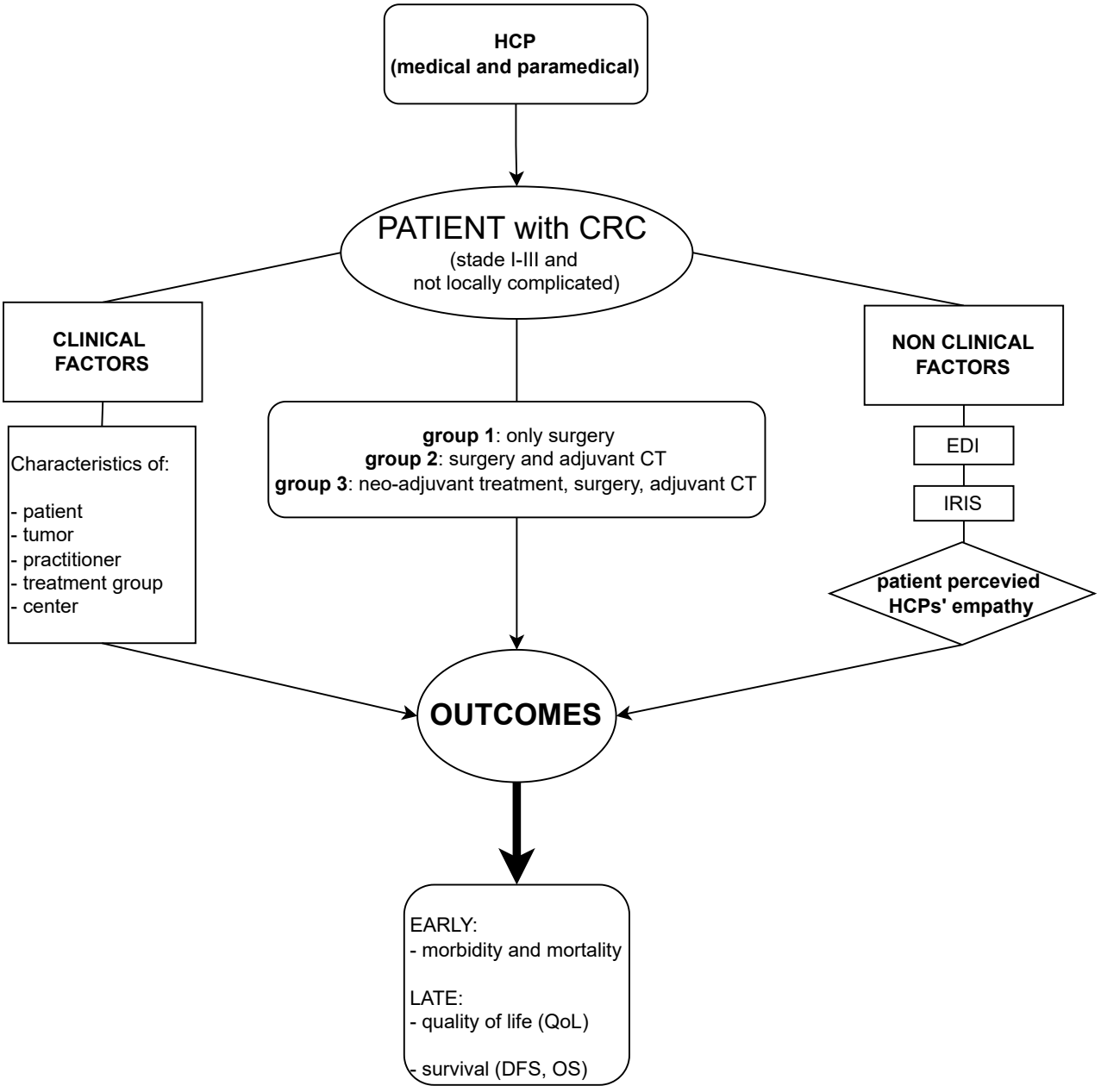
34. Bryant, C. L. C., Lunniss, P. J., Knowles, C. H., Thaha, M. A. & Chan, C. L. H. Anterior resection syndrome. *Lancet Oncol* **13**, e403-408 (2012).

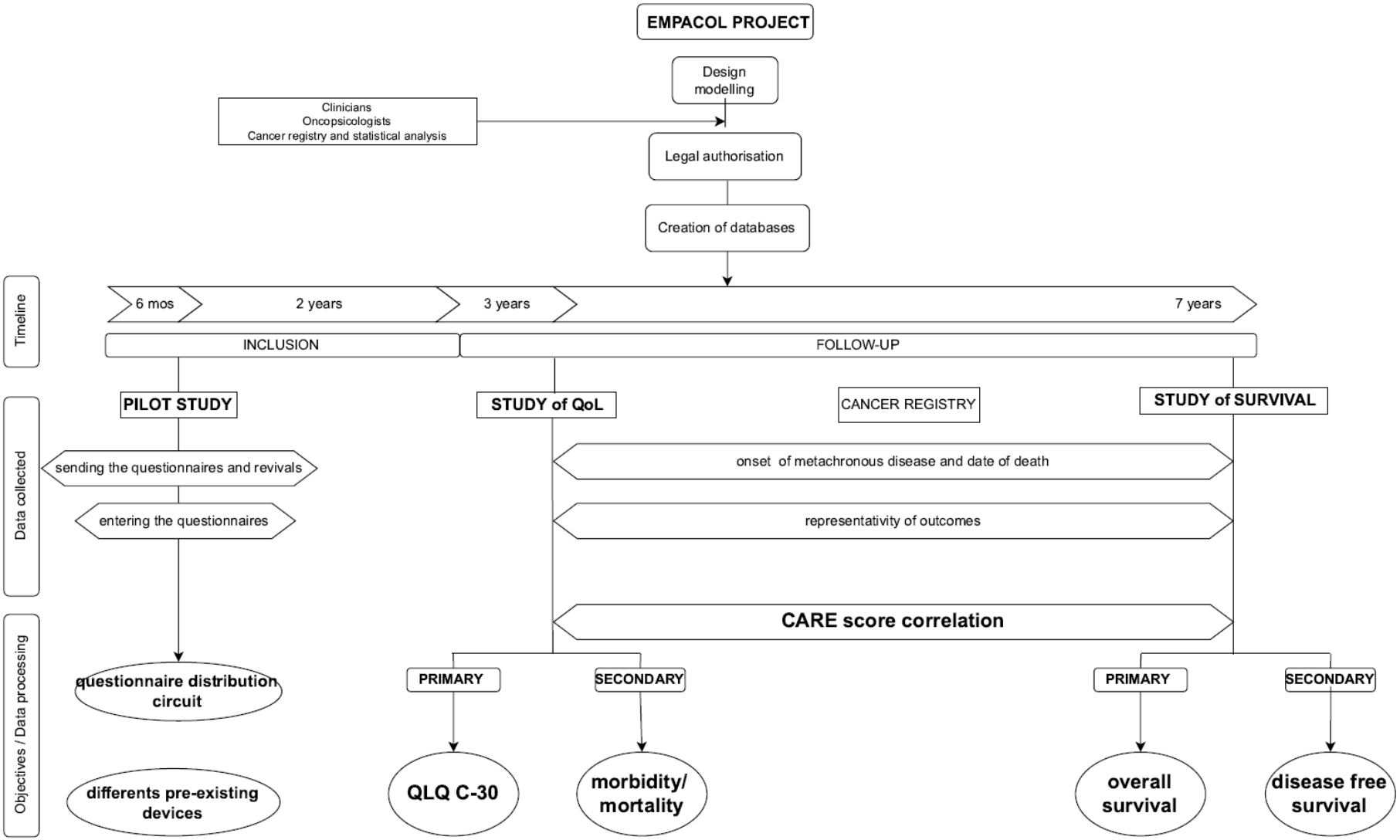
35. Ziv, Y., Zbar, A., Bar-Shavit, Y. & Igov, I. Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. *Tech Coloproctol* **17**, 151–162 (2013).

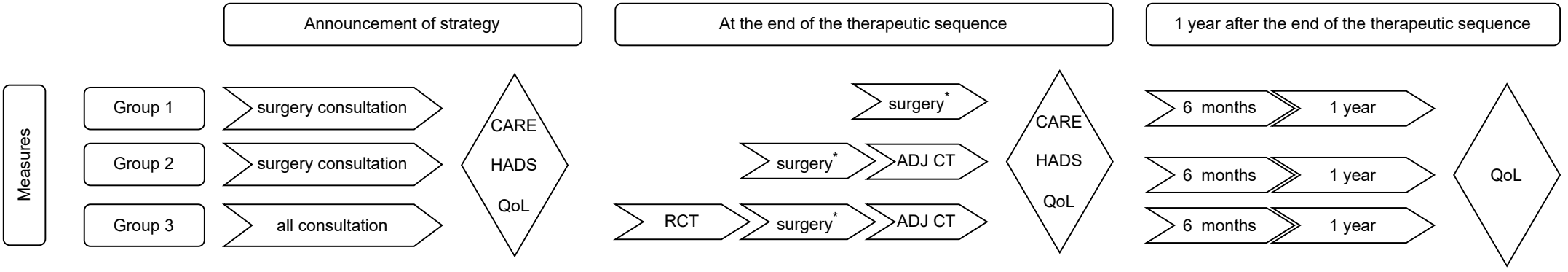
36. Näverlo, S., Gunnarsson, U. & Strigård, K. Rectal cancer patients from rural areas in northern Sweden report more pain and problems with stoma care than those from urban areas. *Rural Remote Health* **21**, 5471 (2021).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml


HCP
(medical and paramedical)
PATIENT with CRC
(stade I-III and
not locally complicated)
CLINICAL
FACTORS
NON CLINICAL
FACTORS
Characteristics of:
- patient
- tumor
- practitioner
- treatment group
- center
group 1: only surgery
group 2: surgery and adjuvant CT
group 3: neo-adjuvant treatment, surgery, adjuvant CT
EDI
IRIS
patient percevied
HCPs' empathy
OUTCOMES
EARLY:
- morbidity and mortality
LATE:
- quality of life (QoL)
- survival (DFS, OS)


EMPACOL PROJECT
Design modelling
Clinicians
Oncopsicologists
Cancer registry and statistical analysis
Legal authorisation
Creation of databases
Timeline
6 mos
2 years
3 years
7 years
INCLUSION
FOLLOW-UP
Data collected
PILOT STUDY
STUDY of QoL
CANCER REGISTRY
STUDY of SURVIVAL
sending the questionnaires and revivals
entering the questionnaires
onset of metachronous disease and date of death
representativity of outcomes
CARE score correlation
Objectives / Data processing
questionnaire distribution circuit
differents pre-existing devices
PRIMARY
SECONDARY
QLQ C-30
morbidity/ mortality
PRIMARY
SECONDARY
overall survival
disease free survival


Announcement of strategy
At the end of the therapeutic sequence
1 year after the end of the therapeutic sequence
Measures
Group 1
Group 2
Group 3
surgery consultation
surgery consultation
all consultation
CARE
HADS
QoL
surgery*
surgery*
ADJ CT
RCT
surgery*
ADJ CT
CARE
HADS
QoL
6 months
1 year
6 months
1 year
6 months
1 year
QoL

BMJ Open

The role of empathy in the outcomes of colorectal cancer: protocol for a population-based study in two areas in France (EMPACOL project)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066559.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Oct-2022
Complete List of Authors:	Mulliri, Andrea; CHU Caen, Lelorain, Sophie; University of Lille, Psychology, Cancer care Bouvier, Véronique; Centre Hospitalier Universitaire de Caen Bara, Simona; CH du Cotentin Gardy, Josephine; Centre Francois Baclesse Centre de Lutte Contre le Cancer Grynberg, Delphine; Université de Lille MORELLO, Rémy; CHU Caen, Unité de biostatistique et recherche clinique Alves, Arnaud; CHU Caen Dejardin , Olivier; Centre Hospitalier Universitaire de Caen, INSERM U1086 Anticipe
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health services research
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Colorectal surgery < SURGERY

SCHOLARONE™
Manuscripts

The role of empathy in the outcomes of colorectal cancer: protocol for a population-based study in two areas in France (EMPACOL project)

Mulliri Andrea
dr.andreamulliri@gmail.com
https://orcid.org/0000-0002-0333-8651
Department of Digestive Surgery, University Hospital of Caen, Avenue de la Côte de Nacre, CEDEX, 14033 Caen, France.
ANTICIPE U1086 INSERM-UCN, Centre François Baclesse, 14000 Caen, France

Lelorain. Sophie
sophie.lelorain@unil.ch
University of Lausanne Switzerland. Center for Research in Health, Aging and Sport Psychology (PHASE).

Bouvier Véronique
veronique.bouvier@unicaen.fr
ANTICIPE U1086 INSERM-UCN, Centre François Baclesse, 14000 Caen, France
Calvados Digestive Cancer Registry, University Hospital of Caen, 14000 Caen, France
Epidemiology Research and Evaluation Unit, Department of Research, University Hospital of Caen, Avenue de la Côte de Nacre, CEDEX, 14033 Caen, France

Bara Simona
simona.bara@ch-cotentin.fr
Hospital Center of Contentin, France

Gardy Josephine
josephine.gardy@inserm.fr
ANTICIPE U1086 INSERM-UCN, Centre François Baclesse, 14000 Caen, France
Calvados Digestive Cancer Registry, University Hospital of Caen, 14000 Caen, France

Grynberg Delphine
delphine.grynberg@univ-lille.fr
CNRS, UMR 9193 - SCALab, University of Lille, France.

Morello Remy
morello-r@chu-caen.fr
Public Health Unit, University Hospital Center Côte de Nacre, Caen, France

Alves Arnaud
alves-a@chu-caen.fr
Department of Digestive Surgery, University Hospital of Caen, Avenue de la Côte de Nacre, CEDEX, 14033 Caen, France.
ANTICIPE U1086 INSERM-UCN, Centre François Baclesse, 14000 Caen, France
Calvados Digestive Cancer Registry, University Hospital of Caen, 14000 Caen, France.

Dejardin Olivier
olivier.dejardin@unicaen.fr
ANTICIPE U1086 INSERM-UCN, Centre François Baclesse, 14000 Caen, France

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Correspondence to:
Mulliri Andrea
dr.andreamulliri@gmail.com

Keywords: empathy, colorectal cancer, treatment, outcomes

ABSTRACT

Introduction

The EMPACOL project aims to investigate the link between healthcare professionals' (HCPs) empathy and the results of the curative treatment of non-metastatic colorectal cancer (CRC).

Methods and analysis

EMPACOL will be an observational multicentric prospective longitudinal study. It will cover eight centers comprising patients with non-metastatic CRC, uncomplicated at diagnosis in two French areas covered by a cancer register over a two-year period. As estimated by the two cancer registries, during the two-year inclusion period, the number of cases of non-metastatic CRCs was approximately 480. With an estimated participation rate of about 50%, we expect around 250 patients will be included in this study. Based on the curative strategy, patients will be divided into three groups: group 1 (surgery alone), group 2 (surgery and adjuvant chemotherapy), and group 3 (neo-adjuvant therapy, surgery and adjuvant chemotherapy). The relationship between HCPs' empathy at the time of announcement and at the end of the strategy, quality of life (QoL) one year after the end of treatment, and oncological outcomes after five years will be investigated. HCPs' empathy and QoL will be assessed using the patient-reported questionnaires, Consultation and Relational Empathy (CARE) and European Organisation for Research and Treatment of Cancer QoL (EORTC QLQ-C30), respectively. A relationship between HCPs' empathy and early outcomes, particularly digestive and genitourinary sequelae, will also be studied for each treatment group. Post-treatment complications will be assessed using the Clavien Dindo classification. Patients' anxiety and depression will also be assessed using the HADS questionnaire.

Ethics and dissemination

The Ethics Committee of the University Hospital of Caen and the Ethics Committee (ID RCB: 2022-A00628-35) have approved the study. Patients will be required to provide oral consent for participation. Results of this study will be disseminated by publication in peer-reviewed journals.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Study registration number

NCT05447611.

Strengths and limitations of this study

- Multicenter and prospective longitudinal design with a multidisciplinary research group to address functional sequelae, socio-territorial inequalities, and empathy, as well as the impact of clinical and non-clinical factors on CRC.
- Supervision of the cancer registry to ensure that the results are representative.
- However, a CARE score threshold is lacking in the literature.
- Additionally, the CARE score does not include an important dimension associated to empathy: the reassurance by HCPs to patients that they will do their very best for them.
- Temporal and spatial heterogeneity between clinical information and questionnaire completion is another limitation.

INTRODUCTION

Epidemiology of colorectal cancer

Colorectal cancer (CRC) remains a public health problem. There were an estimated 43,336 new cases of CRC in France in 2018. This makes it, among solid tumors, the third most common cancer in men and the second most common in women. With 17,117 deaths in 2018, CRC is the second leading cause of cancer death in men and the third leading cause of death in women. The prognosis of CRC has improved significantly over the past 20 years[1],[2]. For patients with colon cancer (CC), a five-year survival rate ranges from 92% for stage I to 11% for stage IV. The multidisciplinary strategy for rectal cancer (RC) has been shown to reduce the five-year local recurrence rate to less than 10%, and increase the five-year overall survival (OS) rate beyond 50%[3].

Colorectal cancer management

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Although the term “colorectal cancer” is commonly used, both multimodal treatment and functional sequelae are not the same for colon and rectal cancer[4]. For forms that are neither metastatic nor locally complicated (non-hemorrhagic, without occlusion or perforation) at the time of diagnosis, surgical oncologic resection (colectomy or proctectomy) represents the cornerstone of treatment with curative intent[5]. As suggested by recent French guidelines[6], surgery is preceded by neo-adjuvant treatment for locally advanced subperitoneal RC. Adjuvant chemotherapy (ADJ CT) is recommended in case of lymph node involvement (stage III) or vascular/lymphatic invasion, peri-nerve, or tumor budding. The short-term outcome of surgical resection is generally reported by mortality rates and morbidity using the Dindo-Classification score assessed on the 90th postoperative day[7]. Since the 2000s, the three-month mortality of CRC patients, regardless of surgical treatment, has decreased significantly, from 15.8% to 11.3%[8].

Both OS and recurrence-free survival are usually the parameters for assessing long-term oncological outcomes. Although OS has increased significantly over time in all European regions[9], the five-year OS rate for both CC and RC depends on lymph node status (N) and cancer stage (T)[10].

Due to the significant improvement in prognosis, the functional dimension of CRC treatment has now become inseparable from carcinologic imperatives[11]. Historically, functional sequelae have long been considered inherent to the carcinologic nature of the surgical resection and are hardly avoidable. While prevalence and predictive factors are different depending on colonic or rectal location[12], functional sequelae (i.e., digestive and/or genitourinary sequelae) may significantly impair their quality of life (QoL).

Quality of life

While QoL remains a priority among CRC treatment outcomes, as outlined in Axis 2 of the latest 10-year strategy 2021-2030 PLAN CANCER FRANCE, little is known regarding the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

evolution of QoL over time in patients operated on for CRC[13]. Most QoL scores drop significantly in the early postoperative period. Surgery, especially total mesorectal excision in RC, significantly reduced patients' QoL[12]. Of all digestive cancer removals, proctectomy for RC carries the greatest risk of functional sequelae and impaired QoL.

Among the functional sequelae observed, the definitive stoma in case of abdominoperineal excision and digestive sequelae in sphincter conservation represent the two main risk factors that potentially alter QoL.

Globally, CC patients have less disabling outcomes compared to patients who have undergone RC surgery[4]. Many side effects are reported in case of ADJ CT. Some toxicities persist after discontinuation of treatment, which may result in changes in patients' QoL.

Role of empathy in care

In human sciences and even clinical settings, the precise definition of empathy is a subject of ongoing academic debate[14–16]. Empathy is often considered one-dimensional, but recent work has demonstrated that a multidimensional view of the concept is also conceivable in oncology[17,18]. Empathy is considered essential for the building and continuation of the therapeutic patient-healthcare professional (HCP) relationship.

In a clinical setting, empathy involves an ability to[19]:

-understand the patient's situation, perspective, and feelings

-communicate this understanding and verify its accuracy

-act on this understanding with the patient in a helpful way (joint planning of an optimal therapeutic strategy).

A systematic literature review suggested a positive association between HCPs' empathy and a variety of positive cancer patient outcomes[20], including increased satisfaction with care and treatment adherence, decreased psychological distress, and improved QoL. Patient perception

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of physician empathy is largely explained by patient and clinical variables[21]. Unmet patient needs are strongly and negatively associated with low perceived empathy.

Empathy must be evaluated during several key moments of the care pathway to study the trajectories of perceived empathy and link between these trajectories and the outcomes of interest. For example, patients with CRC requiring first-line CT present with major concerns at the time of the CT education session as compared to patients with other tumor forms[22].

The sole retrospective study, that examined the link between empathy and survival in oncology, found discordant results, depending on when empathy was assessed[23].

To the best of our knowledge, no prospective study has specifically examined the relationship between patient-perceived empathy at each stage of a treatment sequence and CRC outcomes.

Hypothesis and objectives

The main objective of the EMPACOL project is to investigate, in non-metastatic CRC patients, a possible correlation between patients' perception of HCPs' empathy and survival (OS and disease-free survival, DFS).

The secondary objective of this study is to evaluate the relationship between patients' perception of HCPs' empathy and QoL and morbidity and mortality in patients treated for curative non-metastatic CRC.

We expect to find a negative correlation between HCPs' perceived empathy and morbidity/mortality and a positive correlation between empathy and an improvement in both functional outcome and QoL one year after treatment.

Additionally, we seek to verify if a positive correlation exists between patients' perceived empathy and survival rate (OS, DFS) five years after completion of treatment received.

METHODS AND ANALYSIS

Study design

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

EMPACOL is a descriptive, longitudinal, and multicenter prospective project in two French areas covered by a cancer registry. The project was approved by the French committee for the protection of persons (CPP; n° RCB: 2022-A00628-35).

All investigators will conduct this study in accordance with the Declaration of Helsinki.

Eight CRC centers, including both university hospitals and cancer centers, have agreed to include 50 to 100 patients who will receive curative treatment between 01/01/2023 and 01/01/2025, with the aim of conducting and reporting multicenter studies on the theme of patients' perception of HCPs' empathy, QoL, and survival.

Taking into consideration clinical factors, EMPACOL will evaluate, among non-clinical factors, using the CARE questionnaire, the impact of patient-perceived empathy on short-term (medical-surgical morbidity of each therapeutic step) and long-term outcomes (QoL, DFS and OS). (fig. 1).

To anticipate and respond to the questions and issues that will be encountered in the EMPACOL project and future studies, we plan to design a prospective multicenter pilot study (fig. 2). This pilot study will be integrated into the EMPACOL project.

Patients will be included prospectively over a six month period. The pilot study aims to find a link between the circuit of the questionnaire adopted by the center and the response rate to the questionnaires. Factors that may influence the response rate will also be assessed.

The proposed questionnaire circuit hypothesizes that the patients of groups 1 and 2 will evaluate patients' perception of HCPs' empathy after the surgical consultation and patients of group 3 will evaluate patients' perception of HCPs' empathy once the patient has met the medical and paramedical team (oncologist, radiotherapist, and surgeon) or once the therapeutic sequence has been validated through a multidisciplinary consultation (MDC). A subsequent measurement of patients' perception of HCPs' empathy will be carried out at the end of the therapeutic sequence. Each assessment of patients' perception of HCPs' empathy will be associated with

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

an assessment of the patient's state of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) (fig. 3).

We expect member centers to indicate when the proposed procedure will pose difficulties in terms of filling, delivery, or collection of patient-reported questionnaires to optimize and streamline the following stages of the EMPACOL project.

For the three therapeutic groups, QoL and patients' perception of HCPs' empathy will be simultaneously evaluated at the time of announcing the strategy. The QoL will be reassessed on the 90th postoperative day for group 1 and at the end of the ADJ CT for groups 2 and 3. Regardless of the therapeutic group, the QoL will be reassessed at six months and one year after the end of treatment (fig. 3). We will examine the link between patients' perception of HCPs' empathy and five-year OS and the occurrence of local recurrence or metastatic pathology (disease free survival; primary objective). Moreover, we will study the link between patients' perception of HCPs' empathy and post operative morbidity/mortality and QoL (secondary objective).

Morbidity/mortality will be evaluated at the end of the therapeutic strategy. The most severe complication will be considered in the analyses (fig. 2). The disease will be considered as metachronous in case of tumor recurrence occurring six months after the diagnosis.

Inclusion criteria

The inclusion criteria will be as follows: patients aged 18 to 80 years, who are French speaking, who are affiliated to a social security system, and who have received a detailed description of the study. Furthermore, the patients must be diagnosed with non-metastatic and uncomplicated CRC (without occlusion/perforation/bleeding), require elective therapeutic management, and not have expressed an unfavorable opinion to participate. The participants must provide their oral consent at the time of consultation, where the proposed treatment strategy will be detailed, along with the delivery of questionnaires.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Written consent will not be required from participants (non-interventional research – NIR/MR-003 - Declaration number 2011519 V0). We will include patients who have a cognitive state capable of understanding and completing the questionnaires (autonomous completion).

Exclusion criteria

We will exclude patients who are minors or older than 80 years, residing in a department outside Calvados or Manche, presenting with a CRC other than adenocarcinoma and all metastatic forms or requiring emergency surgery (perforation, hemorrhage, occlusion), undergoing exclusive endoscopic treatment, or with a missed-CRC discovered after surgery for non-oncological indications.

Additionally, we will exclude patients with another neoplastic disease under treatment and/or evolving, a history of inflammatory bowel disease (Crohn's disease, ulcerative colitis), hereditary diseases predisposing to CRC (Lynch syndrome, familial polyposis), and severe cognitive impairment preventing proper comprehension of the questionnaires. Furthermore, pregnant women will be excluded.

Endpoints and measures

Empathy

Patient-perceived empathy will be assessed using the Consultation and Relational Empathy (CARE) questionnaire that has been validated in cancer care[17]. This is a self-reported 10-point questionnaire with a five-point Likert-type scale ranging from "poor" to "excellent." It has excellent psychometric properties with $\alpha = 0.92$. High scores indicate a higher perception of HCPs' empathy. Three distinct empathic processes will also be considered: "rapport" (items 1-3), "emotional process" (items 4-6), and "cognitive process" (items 7-10).

Quality of life

QoL will be evaluated using the EORTC-QLQ-C30, which is equivalent to other tools, such as the GIQLI (Gastrointestinal Quality of Life Index), in terms of emotional function, but

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

superior in terms of social function[24]. The use of an additional tool is recommended for the assessment of depression in CRC patients[25].

Patient anxiety and depression

This parameter will be evaluated with the HADS[26]. The HADS assesses both symptoms of anxiety and depression, which commonly coexist.

Morbidity and mortality

The severity of medical and surgical complications will be assessed using the Clavien-Dindo grading system[7]. Grade I and II complications involve only pharmacological treatment, while grades III, IV, and V require surgical, endoscopic, or radiological treatment. Complications below grade III will be considered "minor complications," while complications above and including grade III will be considered "major complications," as reported in the literature. For the three groups, postoperative morbidity and mortality will be assessed at 90 postoperative days (C/D90). C/D90 will be associated with the morbidity and mortality of the other therapeutic stages, post adjuvant treatment for group 2 (C/DADJ), and post neoadjuvant treatment (C/DNEOADJ) for group 3; it will also be associated with C/DADJ.

Survival and representativeness of the data collected

All patients diagnosed with CRC during the inclusion period will be included in two specialized digestive cancer registries of North-West France, members of the French network of cancer registries (FRANCIM), departments of Calvados and Manche. The resident population of these well-defined administrative areas was 1,601,928 inhabitants in 2016. Both digestive cancer registries included in the present study have collected exhaustive information on treatments and stage in the framework of the high-resolution study. These registries have worked together for many years and use identical standardized data collection, recording, and validation procedures. Multiple information sources ensure exhaustive collection of study variables. The databases are declared to the National Commission on Information Technology and Civil Liberties (CNIL).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The quality of the data collected is evaluated every four years by Institut National de la Santé et de la Recherche Médicale (INSERM), "Santé Publique France," and Institut National du Cancer (INCa).

Data collection

Socio-demographic and medical information will include gender, age (<60 years, 60–69 years, 70–75 years), education level, marital status, obesity (BMI > 30), active smoking and alcohol use, the American Society of Anesthesiologists (ASA) physical status classification system (I-II versus III-IV), anxious and depressive states (HADS score) of the patient and presentation during the multidisciplinary team meeting, histology and tumor differentiation (grades I, II, and III), surgical approach (laparotomy and/or laparoscopy or robotic), neoadjuvant or adjuvant treatments (type and number of sessions), and site of the primary tumor (colon vs rectum). The forms located at the rectosigmoid junction will be included in the colonic localizations.

Socioeconomic status will be defined using the European Deprivation Index (EDI), which is an ecological and composite indicator included in the census of the European Union's statistics on income and living conditions. For all cases, patient addresses will be geolocalized using the geographic information system (ArcGIS 10.2) and assigned to an "Ilots Regroupés pour L'Information Statistique" (IRIS), a geographic area defined by the "Institut National de la Statistique et des Études Économiques" (INSEE). IRIS is the smallest geographical unit in France, for which census data are available.

Statistical analysis

Quantitative variables will be expressed as mean ± SD, and qualitative variables will be expressed as number of patients and percentages. Regardless of the therapeutic group, the experimental design of the study allows for several measurements to be performed in the same individual during their oncological care and follow-up. Comparisons between the mean scores of the three treatment groups will be made using an analysis of variance (ANOVA) or a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Kruskal-Wallis test, depending on whether the data follow the hypothesis of tested homoscedasticity. Post hoc comparisons will be performed with the Bonferroni correction or Nemenyi test.

The sensitivity and specificity of the CARE score in predicting impact on QoL will be assessed by receiver operating characteristic curves for the score versus groups reporting no/minor or definite/major impact on QoL.

The correlation between the validated CARE questionnaire and the QLQ questionnaire (EORTC's QLQ-C30) will be estimated with Pearson's and Spearman's correlation coefficients and their 95% CI.

The inclusion of data indicating the impact of CARE on QoL will be based on a univariate approach and then a multivariate approach using ad hoc models depending on the nature of the dependent variable (binary or multi-nomial logistic regression or linear regression depending on whether the QoL score is considered qualitative or quantitative). Only variables with $p \leq 0.20$ in the univariate analysis will be included in the multivariate model. This approach will allow the identification of risk factors related to the deterioration of QoL and assessment of their impact. All tests will be two-tailed with a significance level (p) equal to 0.05.

We will use the Kaplan-Meier method to obtain survival curves and a Cox model to assess the impact of CARE score on survival in the three different groups. Hazard ratios (HRs) will be calculated, using semi-proportional Cox hazard models, to assess the effect of the CARE score on survival in patients with nonmetastatic, uncomplicated CRC. The proportional hazard hypothesis will be tested (Schoenfeld's residuals). Variables whose threshold p-value is ≤ 0.20 in the univariate analysis (M0) will be included in the multivariate model (M1). The variable of interest (CARE score) will be used in all models.

All statistical analyses will be performed using StataSE14 (StataCorp LLC, College Station, Texas, USA).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Feasibility

We chose to include patients who had undergone curative treatment over a two-year period for two reasons: the first is physiological, to allow their bowel function to become stable. The second is oncological, to detect local recurrence and/or distant metastases. Consistent with recent literature, we considered differentiating the study population into two groups: those with high perceived empathy (maximum CARE score, which is often the modal value in cancer care) and those without.

We calculated with BiostaTGV that approximately 90 patients in each group, thus 180 in total, would be needed to show clinically significant improvement in QoL or reduction in morbidity with high CARE score (power β 80% and risk α 0.05 bilaterally).

From the two cancer registries, we know that over the two-year inclusion period, the number of nonmetastatic CRCs is approximately 480 cases. With an estimated participation rate of about 50%, we expect around 250 patients will be included in this study.

Patient and public involvement

Patients and the public have not been involved in the design, recruitment or conduct of the study. The results will be disseminated to study participants and to the physicians who included them in the study.

ETHICS AND DISSEMINATION

The institutional review board of the University Hospital of Caen and the ethics committee (CPP Nord Ouest I, June 2022; n° ID RCB: 2022-A00628-35) have approved the study.

Patients will be informed orally (according to non-interventional research - NIR MR-003 - Declaration number 2011519 V0) of the purpose of the research and the course and duration of the study and will provide oral consent. They will be able to exercise their right to withdraw at

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

any time. The medical procedures of this study are in accordance with the recommendations of the Declaration of Helsinki and the law n°2012-300 of March 5, 2012, and its application decree n° 2016-1537 of November 16, 2016. In accordance with the Data Protection Act and Law No. 2002-303 of March 4, 2002, the patient may exercise their right to access and rectify the data collected at any time.

Any modification of the protocol will have to be approved by the CPP. The automated processing of health data complies with the European Regulation of April 27, 2016, on the protection of individuals with regard to the processing of personal data and on the free movement of such data. The coordinating investigator of the study undertakes to keep the source documents for a period of 15 years.

Results of this study will be disseminated by publication in peer-reviewed professional and scientific journals. Participant data will be kept confidential and will not be shared with the public. If there are requests for data sharing for appropriate research purposes, this will be considered on an individual basis after study completion and after the publication of the primary manuscripts.

DISCUSSION

The prognosis of CRC has improved significantly over the past 20 years[1],[2]. Oncological principles[27], the development of minimally invasive techniques[28], and advances in diagnostic accuracy[29] are strongly linked to these outcomes and well described in the recent literature. However, many surviving patients experience functional sequelae (i.e., digestive and/or genitourinary sequelae) that significantly impair their QoL. Both prevalence and predictive factors are different depending on colonic or rectal location[12].

Functional disorders occur frequently following surgery for CC. The incontinence of liquid and solid stool is 24.1% and 6.9%, respectively. The most common symptoms associated with

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

constipation is incomplete and difficult evacuation in about one-third of cases[4]. Major low anterior resection syndrome (LARS) is present in 21.1% of patients[4]. No difference is reported in the prevalence of symptoms according to the type of colectomy[4],[12]. In their systematic review and meta-analysis, Verkuijl et al. included 8418 partial colectomies (4207 right hemicolectomies and 4211 left hemicolectomies/sigmoid colon resection, respectively) and 161 subtotal/total colectomies and concluded that bowel function problems following CC surgery are common, do not improve over time, and are not dependent on the type of surgery[4]. For RC, low rectal resections[30] and neoadjuvant radiotherapy[31] are known to severely impair bowel function. Up to 80% of patients with RC undergo sphincter-preserving surgery[32], without impairing oncological prognosis[6],[33]. Between 50% and 90% of these patients will experience a change in their bowel habits afterwards[34],[35]. Eid et al. found that 65.2% of RC survivors had bowel dysfunction, including 41.3% with major LARS and 80% with genitourinary dysfunction[12]. In addition to the psychological burden related to the tumor pathology and concern about the probability of recovery, it is important to consider the patient's experience of the functional results and its repercussions in terms of QoL, especially in case of complications or poor functional results. One of the worst fears related to surgery is the creation of an ostomy.

Problems related to stoma care, or impaired genitourinary or digestive function are likely to have an impact on the QoL of CRC patients.

Patients' perceived unmet rehabilitation needs during the course of their tumor pathology are associated with decreased QoL. Interventions to reduce cancer patients' perceived rehabilitation needs may improve QoL.

Among non-medical factors, other than socioeconomic and geographic inequalities, rural ostomy patients reported more care-related problems and lower QoL[36].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A 2012 review of the literature suggested links between HCPs' empathy and various positive cancer patient outcomes, such as improved QOL or increased satisfaction with care[20]. Assessment modalities for measuring empathy in medical settings are heterogeneous[20].

The associations between the severity of medical and surgical complications and the perception of surgeon empathy has been studied in esophageal and gastric cancer patients[18]. When patients perceived high empathy, they were less likely to report major complications[18]. Of the three dimensions, "rapport building" and "emotional process" were predictive of major complications. Physician empathy is essential before surgery. It is therefore important to consider the patient's experience.

Thanks to the CARE tool, the EMPACOL project will allow us to evaluate patients' perceptions of medical and paramedical staffs' empathy throughout their care, particularly in the case of complications related to the treatment and its impact in terms of early and late results.

HCPs need to be trained to establish a good relationship with patients, from the time of treatment announcement through the period of oncological surveillance. Further research is needed to understand the mechanisms linking empathy to CRC management outcomes.

To this end, this pilot study will allow us to identify the best channel for distributing the questionnaires, study the clinical and non-clinical factors that may influence respondent and non-respondent rates, and identify a correlation with short-term outcomes in each therapeutic group.

The strengths of the project include:

1) it is the first project to study a correlation between empathy and survival in an oncology setting, using a score translated and validated in the French language ; 2) the multicenter, prospective, and longitudinal design makes this a comprehensive study to evaluate empathy and survival in patients with CRC; 3) the multi-disciplinarity of the research group addresses functional sequelae, socio-territorial inequalities, and empathy and evaluates the impact of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

clinical and non-clinical factors in CRC; 4) the cancer registry will ensure the representativeness of the results.

However, the limitations of the project include:

1) the lack of a CARE score threshold in the literature; 2) the temporal and spatial heterogeneity between clinical information and questionnaire completion; 3) the absence of a specific assessment of the patient's experience with uncertainty and negative events during management, such as tumor progression or treatment-related complications, in the CARE score.

The results of the pilot study will therefore help refine the methodological tools that will be used in the EMPACOL project, which aims to find a correlation between the CARE score and long-term outcomes (QoL and survival). The representativeness of the data collected and results of the EMPACOL project will be studied under the supervision of the cancer registries that cover the two departments considered for patient inclusion.

Repeated measurements of perceived empathy, in relation to the treatment received, in the same individual and a follow-up of their evolution over time will make it possible to understand how to facilitate learning, encourage its practice in daily clinical attitudes, and promote the development of empathy in the training of all actors in the caregiver-patient relationship. Obtaining and validating an empathy score, thanks to future studies, will allow a better appreciation of the role of all non-clinical factors in the results in the oncological environment and will open the way to other typologies of cancer.

This project is original as it goes beyond the impact of clinical factors in the outcomes of curative treatment of CRC. The multidisciplinary collaboration and cross-cutting competencies within our research group, functional sequelae, socio-territorial inequalities, and empathy will help us better understand the impact of non-medical factors and role of empathy in the curative treatment of CRC. The prospective and longitudinal nature of this project will allow us to comment on the representativeness of the data collected and results obtained.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

** ** **

Contributors
Study conception and design: AM, SL, DG, OD. Intervention design: SL, VB, SB, JG, DG, RM, AA et AM. Analysis of data will be done by AM, OD and RM. AM drafted the work, wich was revised critically for intellectual content by SL and DG. All authors gave final approval of this version to be published.

Funding
None.

Competing interests
None declared.

For peer review only

REFERENCES

1. Ferlay, J. *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* **49**, 1374–1403 (2013).
2. Siegel, R. L. *et al.* Colorectal cancer statistics, 2017. *CA Cancer J Clin* **67**, 177–193 (2017).
3. Cottet, V. *et al.* Incidence and patterns of late recurrences in rectal cancer patients. *Ann Surg Oncol* **22**, 520–527 (2015).
4. Verkuijl, S. J. *et al.* Functional outcomes of surgery for colon cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* **47**, 960–969 (2021).
5. Labianca, R. *et al.* Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* **21 Suppl 5**, v70-77 (2010).
6. Lakkis, Z. *et al.* Management of rectal cancer: the 2016 French guidelines. *Colorectal Dis* **19**, 115–122 (2017).
7. Clavien, P. A. *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* **250**, 187–196 (2009).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8. Iversen, L. H., Ingeholm, P., Gögenur, I. & Laurberg, S. Major reduction in 30-day mortality after elective colorectal cancer surgery: a nationwide population-based study in Denmark 2001–2011. *Ann Surg Oncol* **21**, 2267–2273 (2014).
9. Brenner, H. *et al.* Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. *International Journal of Cancer* **131**, 1649–1658 (2012).
10. Gunderson, L. L., Jessup, J. M., Sargent, D. J., Greene, F. L. & Stewart, A. K. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol* **28**, 264–271 (2010).
11. Alves, A. [Recommendations for clinical practice. Therapeutic choices for rectal cancer. How can we reduce therapeutic sequelae and preserve quality of life?]. *Gastroenterol Clin Biol* **31 Spec No 1**, 1S52-62, 1S95-97 (2007).
12. Eid, Y. *et al.* Digestive and genitourinary sequelae in rectal cancer survivors and their impact on health-related quality of life: outcome of a high-resolution population-based study. *Surgery* **166**, 327–335 (2019).
13. Schmidt, C. E., Bestmann, B., Kuchler, T., Longo, W. E. & Kremer, B. Impact of age on quality of life in patients with rectal cancer. *World J Surg* **29**, 190–197 (2005).
14. Hall, J. A. *et al*. What is clinical empathy? Perspectives of community members, university students, cancer patients, and physicians. *Patient Educ Couns* **104**, 1237–1245 (2021).
15. Sanders, J. J. *et al.* What is empathy? Oncology patient perspectives on empathic clinician behaviors. *Cancer* **127**, 4258–4265 (2021).
16. Håkansson Eklund, J. & Summer Meranius, M. Toward a consensus on the nature of empathy: a review of reviews. *Patient Educ Couns* **104**, 300–307 (2021).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

17. Gehenne, L. *et al.* Testing two competitive models of empathic communication in cancer care encounters: a factorial analysis of the CARE measure. *Eur J Cancer Care (Engl)* **29**, e13306 (2020).

18. Gehenne, L. *et al.* Associations between the severity of medical and surgical complications and perception of surgeon empathy in esophageal and gastric cancer patients. *Support Care Cancer* (2021) doi:10.1007/s00520-021-06257-y.

19. Mercer, S. W. & Reynolds, W. J. Empathy and quality of care. *Br J Gen Pract* **52 Suppl**, S9-12 (2002).

20. Lelorain, S., Brédart, A., Dolbeault, S. & Sultan, S. A systematic review of the associations between empathy measures and patient outcomes in cancer care. *Psychooncology* **21**, 1255–1264 (2012).

21. Lelorain, S. *et al*. How does a physician's accurate understanding of a cancer patient's unmet needs contribute to patient perception of physician empathy? *Patient Educ Couns* **98**, 734–741 (2015).

22. Oguchi, M. *et al*. Measuring the impact of nurse cue-response behaviour on cancer patients' emotional cues. *Patient Educ Couns* **82**, 163–168 (2011).

23. Lelorain, S., Cortot, A., Christophe, V., Pinçon, C. & Gidron, Y. Physician empathy interacts with breaking bad news in predicting lung cancer and pleural mesothelioma patient survival: timing may be crucial. *J Clin Med* **7**, E364 (2018).

24. Schwenk, W. *et al.* Comparison of EORTC quality of life core questionnaire (EORTC-QLQ-C30) and gastrointestinal quality of life index (GIQLI) in patients undergoing elective colorectal cancer resection. *Int J Colorectal Dis* **19**, 554–560 (2004).

25. Aminisani, N., Nikbakht, H., Asghari Jafarabadi, M. & Shamshirgaran, S. M. Depression, anxiety, and health related quality of life among colorectal cancer survivors. *J Gastrointest Oncol* **8**, 81–88 (2017).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

26. Skarstein, J., Aass, N., Fosså, S. D., Skovlund, E. & Dahl, A. A. Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *J Psychosom Res* **49**, 27–34 (2000).

27. Rodríguez-Luna, M. R., Guarneros-Zárate, J. E. & Tueme-Izaguirre, J. Total Mesorectal Excision, an erroneous anatomical term for the gold standard in rectal cancer treatment. *Int J Surg* **23**, 97–100 (2015).

28. Crippa, J. *et al.* Robotic surgery for rectal cancer provides advantageous outcomes over laparoscopic approach: results from a large retrospective cohort. *Ann Surg* **274**, e1218–e1222 (2021).

29. Zhu, G., Wu, Z., Lui, S., Hu, N. & Wu, M. Advances in imaging modalities and contrast agents for the early diagnosis of colorectal cancer. *J Biomed Nanotechnol* **17**, 558–581 (2021).

30. Keane, C., Wells, C., O'Grady, G. & Bissett, I. P. Defining low anterior resection syndrome: a systematic review of the literature. *Colorectal Dis* **19**, 713–722 (2017).

31. Croese, A. D., Lonie, J. M., Trollope, A. F., Vangaveti, V. N. & Ho, Y.-H. A meta-analysis of the prevalence of Low Anterior Resection Syndrome and systematic review of risk factors. *Int J Surg* **56**, 234–241 (2018).

32. Chau, A. *et al.* Toward the end of abdominoperineal resection for rectal cancer? An 8-year experience in 189 consecutive patients with low rectal cancer. *Ann Surg* **260**, 801–805; discussion 805-806 (2014).

33. Rullier, E. et al. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. *Ann Surgery* **241**, 465–469 (2005).

34. Bryant, C. L. C., Lunniss, P. J., Knowles, C. H., Thaha, M. A. & Chan, C. L. H. Anterior resection syndrome. *Lancet Oncol* **13**, e403-408 (2012).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

35. Ziv, Y., Zbar, A., Bar-Shavit, Y. & Igov, I. Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. *Tech Coloproctol* **17**, 151–162 (2013).

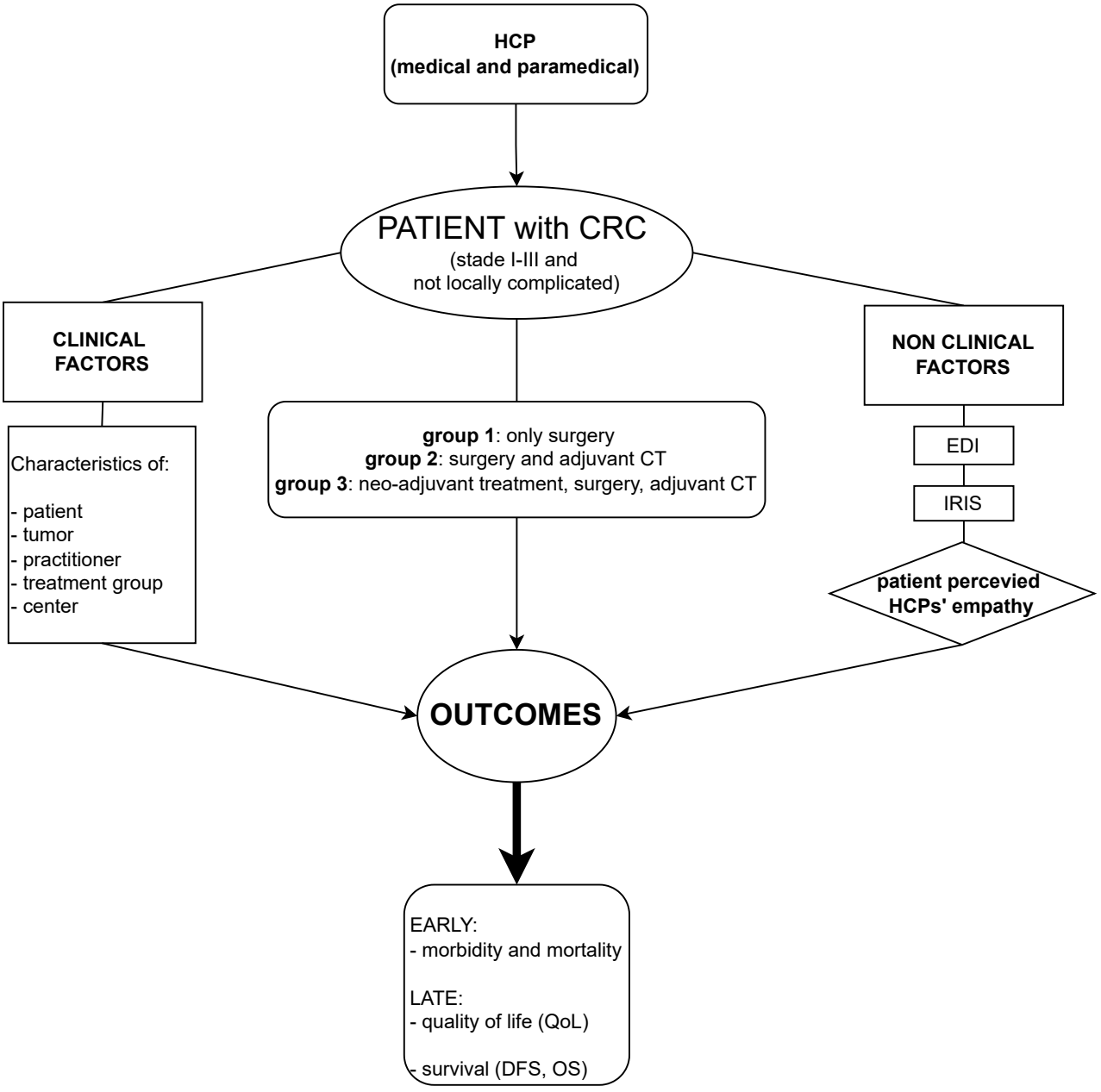
36. Näverlo, S., Gunnarsson, U. & Strigård, K. Rectal cancer patients from rural areas in northern Sweden report more pain and problems with stoma care than those from urban areas. *Rural Remote Health* **21**, 5471 (2021).

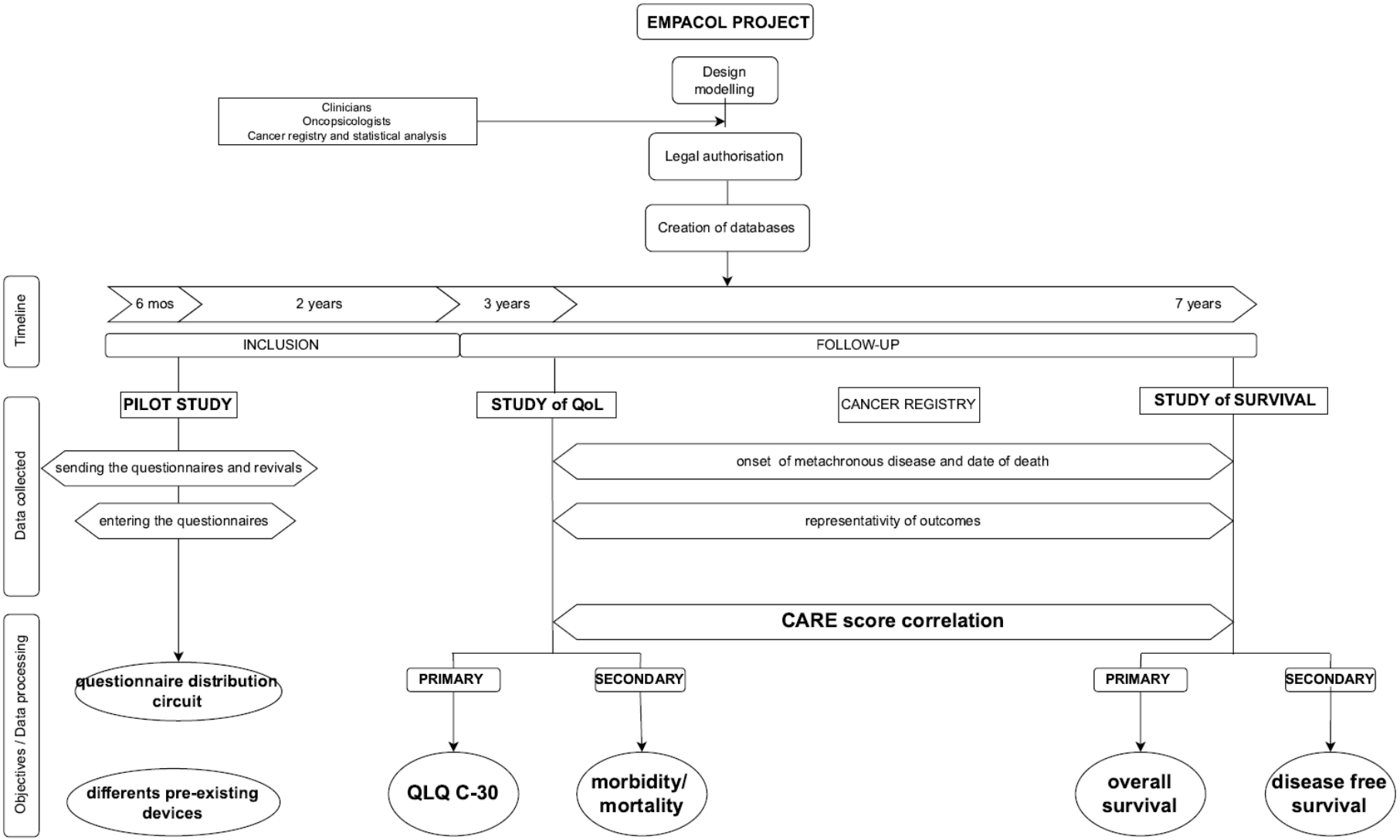
Figure 1. Schematic representation of the factors evaluated
Taking into consideration clinical factors, EMPACOL evaluates, among non-clinical factors, using the CARE questionnaire, the impact of patient-perceived empathy on short-term (medical-surgical morbidity of each therapeutic step) and long-term outcomes (Qol, DFS and OS).

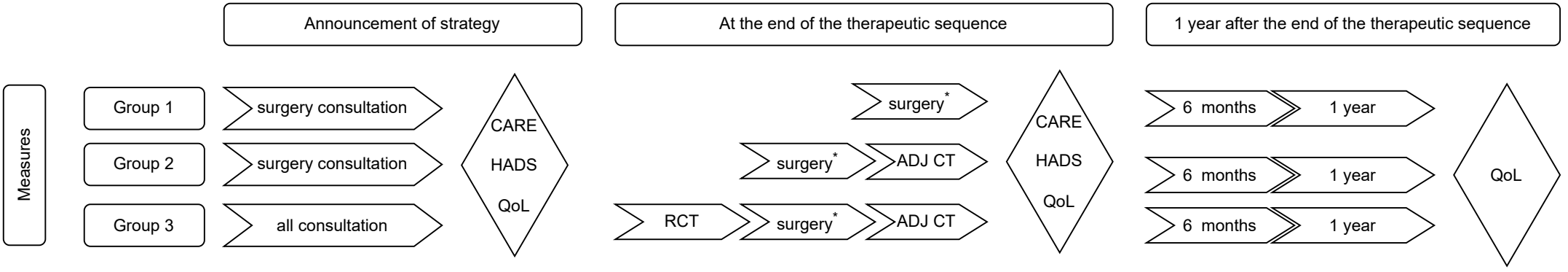
Figure 2. The EMPACOL study design
The EMPACOL project aims to investigate the correlation between the CARE score and QoL at 6 months and 1 year after the end of the therapeutic strategy (secondary objective) and the oncological results in case of metachronous metastatic disease and on the overall survival at 5 years of patients treated with curative intent for stage I-III CRC (primary objective). EMPACOL will start with a pilot study that will allow to study the optimal circuit for the delivery of the questionnaires and to identify the pre-existing systems put in place by the different centers

Figure 3. Proposed questionnaire distribution circuit
For Group 1 and Group 2 patients, the first CARE assessment is performed after the surgical consultation. For patients in group 3, after having met all the medical and paramedical staff. A second CARE score measurement will be performed at the end of the therapeutic sequence. Each CARE score measurement will be associated with an evaluation of the patient's state of anxiety and depression (HADS questionnaire) and QoL (QLQ C-30 questionnaire).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml


HCP
(medical and paramedical)
PATIENT with CRC
(stade I-III and
not locally complicated)
CLINICAL FACTORS
NON CLINICAL FACTORS
Characteristics of:
- patient
- tumor
- practitioner
- treatment group
- center
group 1: only surgery
group 2: surgery and adjuvant CT
group 3: neo-adjuvant treatment, surgery, adjuvant CT
EDI
IRIS
patient percevied HCPs' empathy
OUTCOMES
EARLY:
- morbidity and mortality
LATE:
- quality of life (QoL)
- survival (DFS, OS)


EMPACOL PROJECT
Design modelling
Clinicians
Oncopsicologists
Cancer registry and statistical analysis
Legal authorisation
Creation of databases
Timeline
6 mos
2 years
3 years
7 years
INCLUSION
FOLLOW-UP
Data collected
PILOT STUDY
STUDY of QoL
CANCER REGISTRY
STUDY of SURVIVAL
sending the questionnaires and revivals
entering the questionnaires
onset of metachronous disease and date of death
representativity of outcomes
CARE score correlation
Objectives / Data processing
questionnaire distribution circuit
differents pre-existing devices
PRIMARY
SECONDARY
QLQ C-30
morbidity/ mortality
PRIMARY
SECONDARY
overall survival
disease free survival


Announcement of strategy
At the end of the therapeutic sequence
1 year after the end of the therapeutic sequence
Measures
Group 1
Group 2
Group 3
surgery consultation
surgery consultation
all consultation
CARE
HADS
QoL
surgery*
surgery*
ADJ CT
RCT
surgery*
ADJ CT
CARE
HADS
QoL
6 months
1 year
6 months
1 year
6 months
1 year
QoL