CRP-track protocol

Ref : CHD 065-14

"Evaluation of the predictive character of postoperative CRP on postoperative recovery in patients operated for colorectal resection".

Coordinating Investigator :

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Title: Evaluation of the predictive character of postoperative CRP on postoperative recovery in patients operated for colorectal resection. "CRP-Track study

IRCB registration number: 2014-A01597-40

SIGNATURES

INVESTIGATOR'S SIGNATURE

I have read all the pages of the protocol for the clinical trial sponsored by CHD La Roche sur Yon. I confirm that it contains all the information required to conduct the trial. I undertake to carry out the trial in compliance with the protocol and the terms and conditions defined therein. I undertake to carry out the trial in compliance with :

- the principles of the "Declaration of Helsinki",
- the rules and recommendations of international (ICH-E6) and French (rules of good clinical practice for biomedical research involving medicinal products for human use - decisions of November 24, 2006) good clinical practice.
- national legislation and regulations relating to clinical trials,
- compliance with the EU Clinical Trials Directive [2001/20/EC], a copy of each of which has been provided to me by the sponsor.

I also undertake that the investigators and other qualified members of my team will have access to copies of this protocol and the documents relating to the conduct of the trial to enable them to work in compliance with the provisions contained in these documents.

NAME: Dr. Emeric ABET

Signature: ..... Date :

SIGNATURES

Sponsor :

NAME: Yvon RICHIR, General Manager

Signature: ..... Date :

Principal Investigator :

CENTER : Date :
NAME :

Signature: .....

SUMMARY

Title of study	**"Evaluation of the predictive character of postoperative CRP dosage on postoperative recovery in patients operated for colorectal resection".**
Key words	CRP / Postoperative complication / Length of stay
Responsible for research	**CHD Vendée**
Coordinating investigator (if multicenter study)	Doctor Emeric Abet
Number of centers planned	Bi-centric: La Roche sur Yon / Nantes
Type of study	*Research evaluating routine care*
Study schedule	❖ Total duration: 2 years and 3 months ❖ Recruitment period: 2 years ❖ Follow-up time per patient: 3 months post-operative
Study design	❖ Bi-centric ❖ Uncontrolled ❖ Prospective
Study objectives	**Primary objective:** To show that serum CRP <172mg/L on postoperative day 3this associated with postoperative recovery of less than 5 days (prognostic properties of serum CRP<172mg/L). **Secondary objective(s):** ❖ Show a linear correlation between postoperative CRP value on day 3thand length of hospital stay after colorectal surgery ❖ Show that postoperative CRP measurement prevents readmissions after patient discharge (<5%) ❖ Show that postoperative CRP measurement enables early diagnosis of postoperative complications ❖ Show that a postoperative CRP assay enables early management of postoperative infectious complications ❖ Evaluate the prognostic properties of other alternative markers in this indication (procalcitonin and Lactates) and those of these 3 markers on days 4thand 5th. Investigate whether a combination of the 3 markers provides better prognostic properties.
Number of cases projected	**174 patients**
Schedule of visits and examinations	This schedule corresponds to the usual visits and examinations.

Main selection, inclusion, non-inclusion and exclusion criteria	**Main inclusion criteria :** - *Patient over 18 years of age* - *Programmed hospitalization for colonic resection with anastomosis without permanent or temporary digestive bypass* - *Patient with a preoperative CRP value less than or equal to 172 mg/L* - *Patient who has given his or her consent to participate in the study* - *Patient scheduled to return home after surgery (or convalescent home or non-medical institution)* **Main non-inclusion criteria :** - *Patient under guardianship, curatorship,* - *Person under protection or deprived of liberty* - *Minor patients* - *Patient treated as an emergency* - *Colectomy surgery with digestive bypass or other digestive anastomosis* - *Complex combined surgery (significant associated digestive resection, other surgical procedure that may interfere with postoperative CRP measurement)* - *General inflammatory diseases likely to affect assay values* - *Patients on long-term anti-inflammatory therapy (NSAIDs / corticosteroids / immunosuppressants)* - *Patients unable to understand the proposed study*
Primary endpoint	The de jugement de study composite criterion is: "**Postoperative recovery related to the procedure**" defined as follows: - *Absence of pain >2 on the VAS scale* - *and presence of gaseous intestinal transit* - *And patient autonomy in terms of ambulation and personal care (GIR 5-6)* - *And absence of fever*
Secondary endpoint(s)	- Patient length of stay (in days) - Patient readmission rate within 30 days of discharge - Number of sub-clinical anastomotic fistulas detected on imaging (abdomino-pelvic CT) if CRP > 172 mg/l - Number of re-interventions for postoperative anastomotic complications - Measurements of various biological parameters (serum procalcitonin / lactates / CRP) compared with length of hospital stay and occurrence of postoperative complications.
Statistical analysis	The prognostic properties of serum CRP on day 3^{e}(at a threshold of 172mg/L) for predicting postoperative recovery of less than 5 days will be measured (sensitivity, specificity, positive predictive value, negative predictive value). negative predictive value). The two groups (CRP<172 vs.

	CRP>172) will be compared on all variables. We will also assess the prognostic properties of serum CRP on days 4^{e}and 5, measure those of serum procalcitonin and lactates (on days 3^{e}, 4$^{(e)}$) and 5^{e}) and look for a combination of these markers to improve the prognostic properties of postoperative recovery of less than than 5 days.

LIST OF ABBREVIATIONS

ARC	Clinical Research Associate
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (Advisory Committee on the Processing of Health Research Information)
CRF	Case Report Form (observation booklet)
IDE	State Registered Nurse
INSERM	French National Institute for Health and Medical Research
TEC	Clinical Study Technician
GNEDS	Nantes Group for Health Ethics
RNI	Non-interventional research

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INTRODUCTION

The aim of this study was to evaluate the prognostic character of inflammatory marker assays (CRP, procalcitonin and venous lactates) on postoperative recovery after colorectal surgery. Over the past two decades, the management of patients undergoing colorectal resection has evolved considerably. Peri-operative management has been simplified, with no systematic drainage, no gastric tube, early resumption of feeding and rapid mobilization of patients. This modern approach to digestive surgery makes hospitalization simpler, reducing the length of time patients spend in hospital without increasing the risks, morbidity and peri-operative mortality. Most surgical teams have successfully implemented fast-track surgery. However, some patients will not be able to benefit from this approach because of postoperative events (infectious complications between 10 and 15%), prolonged ileus (between 10 and 20% of cases) or decompensation of an underlying co-morbidity. There are currently no predictive factors for early postoperative recovery. This study assesses the prognostic character of biological inflammatory parameters (CRP, Pro-calcitonin, lactates) on postoperative recovery, using assays at D3, D4 and D5. The stakes are twofold: to enable hospital beds to be planned in care facilities, and to improve individual patient management.

1. RATIONALE FOR THE STUDY

Colonic and rectal resections account for the majority of hospitalizations in visceral surgery departments. Colorectal cancer and diverticular disease are the main indications for colorectal surgery. The length of hospital stay after colorectal resection (for cancer or benign pathology) is conditioned by two main parameters: the patient's autonomy in terms of bowel movements and eating, and the physical ability to ambulate; and the need for in-hospital monitoring of the critical risk period for postoperative bleeding or infectious complications. It therefore depends on factors linked to the patient and the procedure itself.

Among procedure-related parameters, postoperative pain, induced inflammatory reaction, postoperative ileus and the occurrence of infectious complications (surgical site infection, anastomotic fistula, deep abscess, postoperative peritonitis) are the parameters correlated with a longer hospital stay.

In addition, most surgical teams involved in colorectal resections have recently set up early postoperative rehabilitation programs (Fast-track), with a view to optimizing postoperative recovery for patients, but also reducing the length of hospital stay. For selected patients, a 48-hour hospital stay is possible for a surgical colectomy. The patient is discharged from hospital before any bowel movements are resumed. One of the limitations of these programs is the absence of predictive parameters for complications, which would encourage prolonged inpatient monitoring. Similarly, there are no negative predictive factors that would enable patients to be discharged early and safely. At present, the average length of hospital stay for a patient undergoing colorectal resection is 10 days, with little variation between facilities. This compares with 15 days in the 1990s. Early rehabilitation programs published in the literature, without going as far as 48 hours in an authoritarian way, reduce this duration from 3 to 5 days, even before patients resume intestinal transit, with a postoperative readmission rate of around 20%.

In this context, the definition of biological markers predictive of complications and prolonged hospital stay is a challenge for the future, with the aim of anticipating patients' postoperative recovery and the occurrence of complications.

CRP is a serum protein synthesized exclusively by the liver and secreted in situations of systemic inflammation. It plays a role in innate immunity, activating serum complement and promoting phagocytosis in inflammatory foci. At

Due to its short half-life, CRP represents an early non-specific marker of inflammation. In the context of abdominal surgery, and colorectal surgery in particular, CRP has been shown to correlate negatively with the occurrence of postoperative events (1). While elevated CRP is not predictive of complications, a low postoperative serum CRP level is correlated with the absence of complications such as anastomotic fistula (average frequency 10% after colorectal resection). Concerning the best time for this evaluation, whether the assay is performed on the 3rd, 4th or 5thpostoperative day, the negative predictive value is identical (80%), taking the value of 172 mg/L as the threshold. In addition to the occurrence of infectious complications, CRP has also been correlated with duration of surgery, intraoperative blood loss and severity of surgical trauma. To date, other biological markers of systemic inflammation or tissue distress, such as serum pro-calcitonin and venous lactates, have not been evaluated in this specific indication, but are of interest to teams looking for early markers of postoperative complications.

The aim of our study is to assess the value of systematic serum CRP / Pro-calcitonin / Venous lactate measurement in the postoperative period as a predictor of recovery and length of hospital stay. This preliminary routine care study should enable patients' hospitalization and safe return home to be planned.

The project's originality is twofold: from a scientific point of view on the one hand, and from a care organization point of view on the other. From a scientific point of view, CRP, which is already used in current clinical practice, has not been evaluated with a view to modulating the length of hospital stay. Yet this marker is linked to the main vectors of inflammation in digestive surgery (ileus and septic complications). Our work will therefore enable us to define an early marker of postoperative recovery that could modify the medical management of the post-operative period (removal of drains, earlier resumption of feeding). Our study will also enable us to compare different inflammatory markers that can be measured but are not routinely used in this indication.

In terms of care organization, although outpatient surgery is playing an increasingly important role in the management of digestive surgery patients, there are still areas where conventional hospitalization is unavoidable. Nevertheless, the length of hospital stays has been considerably reduced over the last 10 years, without increasing perioperative morbidity. In order to generalize the effort to reduce hospitalization, we need simple, reproducible parameters that predict postoperative recovery time and complications. In addition, optimizing the management of care facilities (beds conventional hospitalization) requires to forecast and to anticipate the duration

for each patient undergoing scheduled surgery. In this context, the originality of our study lies in the evaluation of a low-cost marker already used routinely on an empirical basis in the post-operative follow-up of patients undergoing digestive surgery.

Bibliographical references are given in the appendix.

2. OBJECTIVES AND EVALUATION CRITERIA

2.1. MAIN OBJECTIVE AND EVALUATION CRITERIA

2.1.1. Main objective

To show that a serum CRP <172mg/L on the 3rdpostoperative day is associated with a postoperative recovery of less than 5 days (evaluation of the prognostic properties of a serum CRP<172mg/L).

2.1.2. Primary endpoint

The primary endpoint of the study was a composite criterion: "Postoperative recovery related to the procedure". This criterion is defined as follows:

- Absence of pain >2 on the VAS scale
- Presence of gaseous intestinal transit
- Patient autonomy in terms of ambulation and personal care (GIR 5-6)
- Absence of fever

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objective(s)

- Show a linear correlation between postoperative CRP value on day 3thand length of hospital stay after colorectal surgery.
- Show that postoperative CRP measurement prevents readmissions after patient discharge (<5%)
- Showing that a postoperative CRP assay enables early diagnosis of postoperative complications
- Demonstrate that a postoperative CRP assay enables early management of postoperative infectious complications
- Evaluate the prognostic properties of other alternative markers in this indication (pro-calcitonin and venous lactates) and those of these 3 markers on days 4thand 5th. Investigate whether a combination of the 3 markers provides better prognostic properties.

2.2.2. Secondary endpoint(s)

- Patient length of stay (in days)
- Patient readmission rate within 30 days of discharge

- Number of sub-clinical anastomotic fistulas detected on imaging (abdomino-pelvic CT) if CRP > 172 mg/l
- Number of re-interventions for postoperative anastomotic complications
- Comparison of various biological parameters (serum pro-calcitonin / Lactates / CRP) with length of hospital stay and occurrence of postoperative complications.

3. STUDY POPULATION

3.1. DESCRIPTION OF THE POPULATION

All adult patients seen in a surgical consultation and scheduled for colonic or rectal resection with restoration of unprotected digestive continuity could be included in the study.
Given the activity of the 2 centers concerned, 174 patients out of an annual total of 230 will constitute the study population.

3.2. INCLUSION CRITERIA

Main inclusion criteria :

- Patient over 18 years of age
- Programmed hospitalization for colonic resection with anastomosis without permanent or temporary digestive bypass
- Patient with preoperative CRP less than or equal to 172 mg/L
- Patient having given his or her consent to participate in the study
- Patient scheduled to return home after surgery (or convalescent home or non-medical institution)

3.3. NON-INCLUSION CRITERIA

Main criteria for non-inclusion :

- Patient under guardianship, curatorship,
- Person under protection or deprived of liberty
- Minor patients
- Patients under emergency care
- Colectomy surgery with digestive bypass or other digestive anastomosis
- Complex combined surgery (significant associated digestive resection, other operative procedure that may interfere with postoperative CRP determination)
- General inflammatory diseases likely to affect assay values
- Patients on long-term anti-inflammatory therapy (NSAIDs / corticosteroids / immunosuppressants)
- Patients unable to understand the proposed study

4. STUDY PROCEDURE

4.1. GENERAL RESEARCH METHODOLOGY

The research has the following characteristics:

- Pathophysiological study
- **Bi-centric** study,
- **Uncontrolled** study,
- **Prospective** study
- **Routine care** study

4.2. STUDY AND ANALYSIS TECHNIQUES

4.2.1. Detailed description of evaluation parameters

The primary endpoint is the CRP blood test. This assay is routinely performed at D3 and D5 post-op in all medical analysis laboratories. It meets reference assay standards in individuals with no inflammatory syndrome (normal value < 5 mg/l). In the context of a surgical operation or during which an inflammatory syndrome is systematically present, the CRP value rises. Taking into account a threshold value of 172 mg/l corresponds to a value evaluated in the literature as predictive (if below this value) of the absence of anastomotic complication. We retained this value as a threshold predictive of overall postoperative recovery for patients.
Our primary endpoint (postoperative recovery) is composite, to correspond as closely as possible to the definition of postoperative recovery (patient fit for discharge). To avoid the pitfall of patients waiting for a convalescent facility (patients alone at home), the sole criterion of "length of hospital stay in days" did not seem relevant to us for assessing this recovery. We therefore included in the definition all the parameters that group together post-operative recovery: pain, transit, absence of fever and patient autonomy. This defines a composite criterion, the main judgment criterion.

4.2.2. Description of techniques and analyses

Assays of the various biomarkers included in the study will be performed pre-operatively (for CRP) as well as on day $3^{(th)}$post-operatively and on days $4^{th}$and 5^{th}.
CRP, pro-calcitoninemia and blood lactates are performed according to the standards of the laboratories concerned for hospitalized patients.
As part of standard practice, CRP is measured at D3 and D5 post-op, but not systematically at D4 post-op.
To avoid any bias in the analysis of results, CRP assays should also be performed pre-operatively.

Pro-calcitonin and venous lactate assays are not routinely performed in this specific indication.
Samples will be transported according to the usual procedure applied in the respective departments.

These assays require a blood sample to be taken outside standard practice on D4 (not routinely performed, unless there is the slightest clinical doubt).

*A total of **4** additional blood tubes will be required.*
Pre-operatively: CRP determination is performed on the same tube as the standard pre-operative ionogram - no additional tube is required.
*At D3: **1** additional **tube** for venous lactates, as CRP is performed routinely and pro-calcitonitis can be measured on the same tube as CRP.*
*At D4: **2** additional **tubes**: 1 tube for venous lactates, 1 tube for CRP and pro-calcitonin*
*At D5: **1** additional **tube** for venous lactates, as CRP is performed routinely and pro-calcitonin can be measured on the same tube as CRP.*

4.3. STUDY SCHEDULE

Patients seen in the pre-operative consultation will be informed of the study. The information letter will be handed out during this consultation. Inclusion in the study will take place before the operation (the day before or the day of the operation) by confirming that the patient has no objection to taking part in the study.
A CRP assay will be performed preoperatively after the patient has indicated that he/she does not wish to participate.
Following the operation, the postoperative CRP assay will be carried out at the same time as the other assays (pro-calcitonin and lactates) on day 3th, then on days 4thand 5thpostoperatively. In the interim, clinical follow-up of patients was in line with routine management. All postoperative events are recorded in the patient's clinical record.
In the event of a postoperative complication occurring during hospitalization, the assessment and management will be in line with normal patient follow-up, and will be recorded in the patient's record book. These elements will be taken into account in the primary endpoint. Clinical data, biological and imaging tests, and diagnosis will be reported. If a re-intervention is necessary, the report will be attached, as will any medical treatment related to the complication.
In the absence of any particular event, the patient's hospitalization will continue under the same conditions as usual. Every day during hospitalization, the various parameters used in the study analysis will be recorded in the patient's notebook. Biological assay values will also be recorded (samples taken on days 3, 4 and 5). The discharge date will be decided by the surgeon in charge of the patient, independently of the study, but will be recorded in the patient file and the research CRF.
After discharge, the patient will be seen again in a postoperative consultation at 1 month, then at 3 months for the end-of-study visit (usual follow-up). At each visit, a clinical examination will be performed.

STUDY SCHEDULE

Actions	J-30 (Pre-inclusion visit)	J0 (Inclusion visit)	Every day During hospitalization	D3 / D4 / D5	Date of discharge	M1	M3 Study discharge
Patient information	X						
History	X						
Clinical examination	X	X	X	X	X	X	X
Paraclinical examinations	X	X	X	X	X	X	X
Medical procedures (ECG...) Each procedure must be located on a line							
CRP measurement Pro-calcitoninemia Lactatemia	X (CRP only)			X			

4.4. CRITERIA FOR PREMATURE FROM THE OF A PERSON'S PARTICIPATION IN RESEARCH

Please refer to the statistics section for details of the procedures and duration of follow-up for people who have prematurely stopped participating in the study.

There are no criteria for premature termination of a person's participation in research, apart from the patient's death or withdrawal of consent.

5. DATA MANAGEMENT AND STATISTICS

5.1. STUDY DATA COLLECTION AND PROCESSING

5.1.1. Data collection

An observation notebook (CRF) will be created for each patient. All information required by the protocol must be provided in the CRF. It must include the data needed to confirm compliance with the protocol, and all the data required for statistical analysis, and to detect major deviations from the protocol.

Data will be collected on a Clinsight database, developed by the Data Management team of the Nantes University Hospital Research Department.

5.1.2. Data coding

By signing this protocol, the principal investigator and all co-investigators undertake to keep confidential the identities of all patients participating in the study.

The transmission of a person's data for research purposes will only be possible if a coding system is used; the presentation of research results must exclude any direct or indirect identification.

A code will be set up for each patient. This code will be the only information to appear on the CRF, enabling the CRF to be traced back to the patient.
The person in charge of the research will also code the patient data on any documents in his/her possession (reports of imaging or biological examinations, etc.) which are attached to the CRF.
Only the first letter of the subject's surname and first name will be recorded, together with a coded number specific to the study, indicating the center number and the order of inclusion of subjects.
Each investigating center will keep a correspondence file between the study code and the identity of subjects from its own center. None of this direct or indirect identification information will be available for study analysis, and will be kept only at the center concerned.

Most assays are performed on the same tubes as routine assays. Samples will therefore be taken in the same way and at the same time as standard practice samples. Anonymized results will be entered with the other data on the study's general e-CRF.

5.1.3. Data processing

The collection of clinical data will be based on the creation of a clinical database and data entry masks similar to the observation book, in compliance with the protocol and regulations currently in force.
The structure of the database and data entry screens will be approved by the research manager.

5.2. STATISTICS

Name and contact details of analysis manager: Aurélie
Le Thuaut
Clinical Research Unit CHD
Vendée
Bd Stéphane Moreau - Les Oudairies
85925 La Roche sur Yon
aurelie.le.thuaut@chu-nantes.fr

5.2.1. Description of methods statistics planned, including timing of planned interim analyses

Primary endpoint: definition of the prognostic properties of using serum CRP at a threshold of 172mg/L on day 3thto predict postoperative recovery of less than 5 days: Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV). In particular, the NPV will be specifically studied, as it is this value that will associate a better postoperative recovery of less than 5 days with a serum CRP value on day 3^{e}<172mg/L.
A subgroup analysis according to the type of pathology (malignant or benign) will be carried out if the numbers in each group allow it.

The sample will be split into two groups according to serum CRP value on day 3th(cut-off value 172mg/L). Data will be analyzed and compared between these two groups using chi-square tests for categorical variables and Student's t tests for continuous variables, in particular for the variables "readmission after patient discharge",
"postoperative complications" and "postoperative infectious complications".
Linear correlations between serum CRP on day 3^{e}and the following variables will be estimated:

- Length of hospital stay
- Serum CRP on days 4thand 5th
- Procalcitonin on days 3th, 4 and 5$^{(th)}$)
- Lactates on days 3(th) , 4thand 5$^{(th)}$)

The prognostic properties of serum CRP, procalcitonin and lactate will be determined by looking for thresholds t h a t optimize the negative predictive value (the main prognostic criterion of interest).

(the main prognostic criterion of interest), using cost minimization by assigning a cost of 3 for a false negative and a cost of 1 for a false positive.

In order to avoid any bias in the analysis of results, CRP measurement will be performed pre-operatively for all patients.

5.2.2. Statistical justification of the number of inclusions

Determination of the number of subjects required is based on the desired precision of the Negative Predictive Value. Preliminary data are obtained from the article by Singh et al (BJS, 2014). In this article, a meta-analysis is used to determine the prognostic values of serum CRP on anatomical leakage in colorectal surgery.

Based on this article, 72% of patients had a serum CRP below 172 mg/L (patients on whom NPV can be estimated). In addition, the NPV was estimated at 97%. To obtain a precision (half-width of the 95% confidence interval) on the NPV of 3%, we would need 125 patients with a serum CRP below 172mg/L, i.e. 174 patients in total.

5.2.3. Expected level of statistical significance

The expected level of significance is 5%.

5.2.4. Statistical criteria for discontinuation

There are no statistical stopping criteria.

5.2.5. Method from catch in account of missing, unused or invalid data

For the 3-day serum CRP value, in the presence of missing data, no imputation will be performed and the patient will not be analyzed.
For the variable "postoperative recovery of less than 5 days", in the event of missing data, a "worst case" imputation will be performed, leading to these patients being considered as not having had a postoperative recovery of less than 5 days. In the event of a high rate of missing data (>5%) on this variable, a sensitivity analysis will be carried out using different imputation methods (average, multiple imputation, etc.).
No imputation will be performed for other data.

5.2.6. Management of modifications made to initial strategy analysis plan

There will be no changes to the initial strategy analysis plan, but additional analyses may be carried out.

5.2.7. Selection of subjects for analysis

All patients included in the study will be analyzed.

6. SAFETY / ADVERSE EVENTS

The occurrence of an adverse effect related to the patient's care during the present protocol will give rise to a declaration to the appropriate vigilance system (pharmacovigilance, biovigilance, hemovigilance, materiovigilance, etc.).

7. JUSTIFICATION FOR REQUESTING VALIDATION OF RESEARCH IN ROUTINE CARE

Taking all these factors into account, the person in charge of the research qualifies it as ***research in routine care****, since :*

- ✓ *All procedures are carried out in the usual way (biological samples for assessment, clinical data, surgical intervention).*

The research does not involve innovative or obsolete techniques or strategies.

Blood samples will be taken as described in the usual post-operative check-ups.

Additional assays are :

- CRP assays pre-operatively and on D4
- venous lactate and pro-calcitonin determinations on D3, D4 and D5 post-op.

These assays require a blood test to be performed outside standard practice on D4 (not routinely performed, unless there is the slightest clinical doubt).

A total of 4 additional blood tubes will be required.

Apart from these tests, all other aspects of patient management will be identical to standard practice. In particular, the discharge date will be decided by the surgeon in charge of the patient, independently of the study and the results of the assays, but will be recorded in the patient file and the research CRF.

As a result, the particular conditions under which the research is carried out represent negligible constraints for the person undergoing the research. (Article R 1121-3 of the French Public Health Code (CSP), Decree no. 2006-477 of April 26, 2006)

The person in charge of the research will therefore submit the study protocol to the Comité de Protection des Personnes Ouest V de Rennes for a favorable opinion and confirmation of the research's qualification, prior to any implementation of the research, in accordance with article L 1121-1 of the French Public Health Code (CSP), as amended by laws no. 2004-806 of August 9, 2004 and no. 2006-450 of April 18, 2006 relating to public health policy.

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

Each patient's medical data will be transmitted only to the organization to which the person in charge of the research is attached, or to any person duly authorized by the latter, under conditions guaranteeing confidentiality.
If necessary, the organization reporting to the person in charge may request direct access to the medical file in order to verify research procedures and/or data, without breaching confidentiality and within the limits authorized by laws and regulations.

8.2. CONFIDENTIALITY OF DATA

Persons having direct access will take all necessary precautions to ensure the confidentiality of information relating to the persons concerned, in particular as regards their identity and the results obtained.
These persons, in the same way as the investigators themselves, are bound by professional secrecy (under the conditions defined by articles 226-13 and 226-14 of the French penal code).
During or at the end of the research, the data collected on the subjects and transmitted by the investigators will be rendered anonymous.
Under no circumstances may the names or addresses of the persons concerned appear in clear text.
Only the first two letters of the subject's name and the first letter of his/her first name will be recorded, along with a coded number specific to the study indicating the order of inclusion of subjects.

8.3. COMPUTERIZED DATA AND SUBMISSION TO THE CNIL

Data collected during the study will be stored in a computer file in compliance with the French Data Protection Act of January 6, 1978, amended in 2004.

The protocol will be submitted for CCTIRS approval, and the computerized processing will be subject to CNIL authorization.

8.4. TRIAL MONITORING AND QUALITY CONTROL

A Clinical Research Associate (CRA) will visit each site to carry out quality control of the data reported in the case report forms.

The monitoring plan will be defined in consultation between the research team and the institution in charge, according to the objectives of the study and the internal procedure of the research department.

On-site monitoring visits will be organized by appointment with the investigator. CRAs must have access to :
- data collection notebooks for included patients, or the computerized database in the case of electronic observation notebooks
- patients' medical and nursing records

8.5. PROTOCOL AMENDMENTS

An updated version of the amended protocol must be dated. The information note should be amended if necessary.
Any amendment to the study protocol must be notified to the Comité de Protection des Personnes, to ensure that the proposed modifications do not alter the guarantees provided to research subjects.

8.6. INSURANCE

Insofar as the research is qualified as routine care research by the CPP, which means that there is no additional risk associated with the study, the insurance will be that of the establishment responsible for the care (article L. 1142-2).

8.7. PUBLICATION RULES

The center which has included the most patients will occupy the first position in author rank (first author the project leader of the center concerned). Successive ranks will then be assigned according to the number of patients included. The last author will be the other project leader concerned.
A copy of the publication will be given to the CH La Roche-sur-Yon, the study leader, and to the CHU de Nantes, the participating center, which will necessarily be cited.

9. ETHICAL CONSIDERATIONS

9.1. SUBMISSION TO AN ETHICS COMMITTEE

The person in charge of the research undertakes to submit the study project to a Comité de Protection des Personnes (CPP) for an ethical opinion.

9.2. PATIENT INFORMATION

The investigator undertakes to provide the patient with clear and accurate information about the protocol (information note in appendix). He will give the patient a copy of the information note. This will specify the patient's right to refuse to take part in the research and to withdraw at any time. Patients will be able to ask any questions they may have and obtain all the information they need to fully understand the project.

9.3. WRITTEN PATIENT CONSENT

As part of the project, the patient receives an information note containing a signature block, and gives the doctor a signed copy. This copy is kept in the patient's medical file. The patient keeps a copy himself.

LIST OF APPENDICES

- *Listing of investigators*
- *Bibliographical references*
- *Patient information note*
- *Observation booklet*

APPENDIX 1: BIBLIOGRAPHICAL REFERENCES

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APPENDIX 2: PATIENT INFORMATION NOTE

Information note for research participation

"Evaluation of the predictive character of CRP on postoperative recovery in patients undergoing colorectal resection surgery".

Short title: "CRP-track

Investigating physician
Name: .....
Department/institution: .....

Institution Responsible for the research
CHD de la Roche sur Yon - Boulevard Stéphane Moreau, 85 925 La Roche sur Yon
Contact: Unité de recherche clinique du CHD de la Roche sur Yon : Dr Jérôme DIMET
02 51 44 65 64 / jerome.dimet@chd-vendee.fr

This document is given to the patient, whose participation is recorded in the medical record.
A copy is kept outside the medical file, along with the study documents.

Dear Sir/Madam

The Digestive Surgery Department of the Centre Hospitalier Départemental Vendée de La Roche-sur-Yon and the Digestive and Endocrine Surgery Department of the Centre Hospitalier et Universitaire de Nantes are collaborating on a study of the prognostic effect of blood levels of inflammatory markers (CRP, pro-calcitonin and venous lactates) o n postoperative recovery after colorectal surgery.

You are about to undergo colorectal resection surgery, and a number of blood tests will be performed during postoperative monitoring. In addition to standard CRP measurements, we would like to measure other markers such as pro-calcitonin and venous lactates as part of the "CRP-Track" study.
The aim of this study is to determine whether these markers, which are specific to inflammation, could help predict the possible occurrence of postoperative events (surgical site infection or delay in resumption of intestinal transit) and the length of hospital stay following your colorectal surgery.

Why this research?
Ultimately, the aims of this study are to anticipate the length of post-operative recovery after this type of operation, which we know is decreasing; and at the same time, to predict the occurrence of complications.

How will this research be carried out?

This test is carried out on the basis of medical data collected during your usual care.

With your consent, an additional CRP assay will be performed as part of your standard pre-operative blood test.

After your operation, blood samples will be taken as part of your standard post-operative follow-up. With your agreement, CRP, pro-calcitonin and venous lactate measurements will be taken at D3, D4 and D5 post-op.

These assays mean that you will have to take an additional blood sample at D4 post-op, whereas in standard practice you would only have had one at D3 and D5.

This also represents the equivalent of 4 additional blood tubes in total over the 3 days of post-operative follow-up. These extra tubes are needed to perform these assays in addition to your standard biological tests.

Your samples will be destroyed in accordance with the hospital's usual practice.

Your participation in the research will not affect your treatment, with the exception of the blood samples specifically collected.

This research will take place at the Centre Hospitalier Départemental Vendée de la Roche sur Yon and the Centre Hospitalier Universitaire de Nantes.
It is planned to include 174 patients scheduled for colorectal resection surgery over a two-year period.

What are your rights?

The doctor in charge of your care will suggest that you take part in this study, and you are free to accept or refuse without having to justify your decision.
Your treatment will be the same whether or not you take part in this research. Your participation in this research will not generate any additional costs for you.

This research poses no risk to your health. The results will not provide information relevant to your health in particular. They will contribute to the development of knowledge in the field of colorectal surgery, and will need to be confirmed by further clinical studies, to enable the development of new diagnostic methods, and new surgical or therapeutic treatments.

At your request, your doctor can inform you of the overall results of this research.

In order to be carried out successfully, this research requires the computerized processing of your personal data to enable the results to be analyzed. A computer file containing your data will therefore be created. For reasons of confidentiality and to respect your privacy, your data will be systematically coded. Only the healthcare professionals personally in charge of your follow-up will have access to your personal data.

Your data may be transferred to organizations other than CHU de Nantes, in France or abroad. In this case, your identity will be coded and you will not be identified.

In accordance with the law, you have the right to access, oppose and rectify any data stored on your computer, at any time, through your doctor. You also have the right to object to the transmission of data covered by professional secrecy that may be used and processed as part of this

research. You can exercise your rights of access and rectification by contacting the doctor mentioned at the beginning of this document.
This study has been approved by the Comité Consultatif sur le traitement de l'information en matière de recherche (CCTIRS) and authorized by the Commission Nationale Informatique et Libertés (CNIL).
In accordance with the French Public Health Policy Act, this research obtained a favorable opinion from the Comité de Protection des Personnes Ouest V de Rennes on *05/02/2015.*

You are free to accept or refuse to participate in the research presented to you. If you accept, you are free to change your mind at any time without having to justify your decision, and your decision will not prejudice the quality of your care. If you refuse to take part in the research, only the data necessary for your care will be collected and will not be used in the research.

The doctor who proposed the research and gave you all the necessary information verbally can answer any questions you may have.

To be completed by the investigator

Patient's surname/first name ..... Date

information given: ...../...../.....

The patient has not expressed any objection to participation in the study.

Name of investigator:..... Signature of investigator :

APPENDIX 3: OBSERVATION BOOKLET

Parameters entered in the database :

Pre-operative demographic and administrative data:

- First two letters of surname / and first letter of first name / month and year of birth
- Inclusion date
- Date of operation
- Indication (pathology)
- Medical history (heart disease / inflammatory disease / renal failure / respiratory disease / diabetes)
- Usual treatment

Parameters entered the day before surgery :

- Infectious manifestations in the previous 10 days

Procedure parameters :

- Type of surgery (title)
- Type of continuity restoration (surgical set-up)
- Infectious event (surgical contamination)
- Duration of operation
- Approach (laparo / Coelio)

Postoperative parameters (during hospitalization)

- Daily: Temperature / pulse / EVA (in the morning)
- Date of first gas
- Date of first bowel movement
- Date of first rising
- Date of first access to hallway for ambulation (with or without assistance)

- Date of discharge
- Discharge orientation (home or care facility)

Post-operative event

- Infectious event: Date of diagnosis
    - Complementary imaging tests (results attached)
    - Surgical intervention
    - Radiological drainage
- Prolonged Ileus (gastric tube maintained for more than 7 days or gastric tube inserted for more than 7 days)
- Other complication (co-morbidity)

Biological measurements

Preoperative CRP

CRP / Pro-Cal / Lactates D3 D4 D5

Routine laboratory tests postponed:

Hemoglobinemia to D5

Transfusion if necessary White

blood cell count on D5

Postoperative urea / creatinine levels

Visit 1 to 1 month

Clinical examination / Treatment

Visit 2 to 3 months: End of

study Clinical examination /

Treatment

Interim hospital readmission

Occurrence of a SAE (event likely to induce an inflammatory reaction)