



## **LEK CHECK STUDY:**

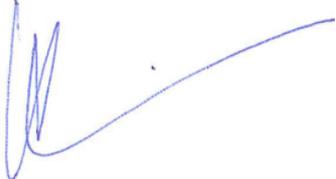
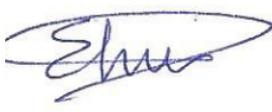
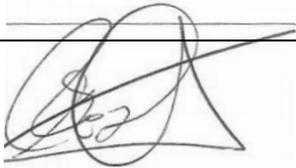
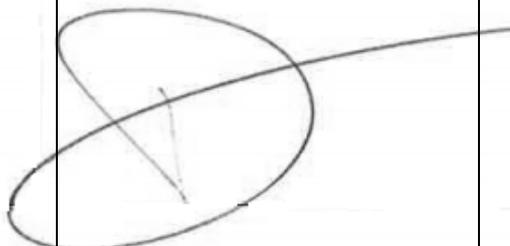
*(previously named **MERCURY** study:*

***MEasurement of Rates of Colorectal anastomotic  
leakage Using a Risk factor Leak  
age Check procedure perioperatively)***

**PROTOCOL TITLE:** LEK CHECK (previously named MERCURY study; measurement of rates of colorectal anastomotic leakage using a risk factor leakage check procedure perioperatively)

<b>Protocol date</b>	<i>20-10- 2016</i>
<b>Short title</b>	<i>LEK CHECK-Study</i>
<b>Version</b>	<i>4.0</i>
<b>Date</b>	<i>12-6-17</i>
<b>Project leader</b>	<i>D E Huisman VU Medical Centre, Amsterdam Department of Surgery d.huisman@vumc.nl</i>
<b>Co author</b>	<i>Dr. S J van Rooijen Maxima Medical Centre, Veldhoven Department of Surgery De Run 4600 5504 DB Veldhoven 0620229373 stefan.van.Rooijen@mmc.nl</i>
<b>Principal investigator</b>	<i>Dr. F. Daams, VU Medical Centre, Amsterdam. Department of Surgery. De Boelelaan 1117 1081 HV Amsterdam +31204444444, pager 7130 F.Daams@vumc.nl</i>
<b>Sponsor:</b>	<i>Board of Directors, VU Medical Centre</i>
<b>Submitter</b>	<i>D. E. Huisman, VU University Medical Center</i>

## PROTOCOL SIGNATURE SHEET

Name	Signature	Date
<p><b>For non-commercial research,</b></p> <p><b>Head of Department</b></p> <p><i>Prof. dr. G Kazemier</i></p> <p><i>VU Medical Centre</i></p> <p><i>Department of Surgery</i></p>		<p>11/1/16</p>
<p><b>Project leader</b></p> <p><i>D E Huisman</i></p> <p><i>VU Medical Centre</i></p> <p><i>Department of Surgery</i></p>		<p>17-12-2015</p>
<p><b>Co author</b></p> <p><i>S J van Rooijen</i></p> <p><i>Maxima Medical Centre</i></p> <p><i>Department of Surgery</i></p>		<p>14-12-2015.</p>
<p><b>Principal investigator</b></p> <p><i>Dr. F Daams</i></p> <p><i>VU Medical Centre</i></p> <p><i>Department of Surgery</i></p>		<p>11/1/16</p>
<p><b>Local Project leader</b></p> <p><i>D. Lips</i></p> <p><i>Jeroen Bosch Ziekenhuis</i></p> <p><i>Department of Surgery</i></p>		

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## SUMMARY

**Rationale:** Colorectal anastomotic leakage (CAL) following colorectal surgery remains surgeons' most feared complication with an incidence varying from 8-13%. Due to CAL, 30-day mortality, readmission rate and Length of hospital Stay (LOS) rise substantially. Worldwide, the main focus of research is directed towards optimization of surgical techniques and treatment of CAL as well determining relevant risk factors. However, little is known regarding possible strategies that can prevent development of CAL. The aim of this study proposal is to identify high risk factors intraoperatively using a Leakage Check procedure, a multifactorial checklist scored with the whole surgical team prior to making a colorectal anastomosis. This could result in an unambiguous protocol to identify high risk patients.

**Primary objective:** Determination of relevant and modifiable perioperative risk factors of Colorectal anastomotic leakage in a Leakage Check procedure, a multifactorial checklist, right before the creation of the anastomosis.

**Study design:** Prospective multi-center observational registration study. Perioperative Leakage Check procedure to register hemodynamic risk factors, postoperatively registration of CAL and postoperative complications.

**Study population:** Adult patients undergoing colorectal surgery with an anastomosis.

**Intervention:** None.

**Main study parameters/endpoints:** Deviating perioperative risk factors.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** There are no risks or additional burden. Benefit for the patient itself is expected since their perioperative status is monitored more securely.

## 1. INTRODUCTION

### **Colorectal anastomotic leakage (CAL)**

In colorectal surgery the only alternative for a stoma is a colorectal anastomosis by reconnecting the two ends of intestine.<sup>1</sup> The problem that this procedure encounters is that this attachment can leak<sup>2</sup>. The consequences of an anastomotic leak are well known amongst surgeons. Symptoms such as abdominal pain, palpitations, fever and a bloated abdomen along with characteristic blood tests, are indicative for urgent return to the operating table for re-opening of the abdomen<sup>3</sup>. The surgery area needs to be washed out and a fecal diversion is necessary otherwise gastrointestinal contents can cause further complications. This is associated with a prolonged stay in the intensive care unit, and a mortality rate of approximately 10% to 15%<sup>4</sup>. In addition, a suture leakage has been associated with an increased local relapse and a reduced survival after colorectal cancer surgery<sup>5,6</sup>. The 30-day mortality as well as the readmission rate and Length of hospital Stay (LOS) rises substantially with CAL, thereby increasing the treatment costs.

Colorectal anastomotic leakage is an important topic in scientific research due to the severe consequences. A number of anastomotic studies resulted in a decline of leakage. Nevertheless, CAL remains a surgeons most feared complication with an incidence varying from 8-13%<sup>7-10</sup>. Main research focus has been directed towards optimization of surgical techniques and determining relevant risk factors.<sup>7</sup> Several studies put a lot of effort in using different materials wrapped around the connection area to prevent leakage<sup>11</sup>. These have not been fully successful until now. Researchers are now aiming at early detection of CAL to intervene as quickly as possible<sup>12-16</sup>, however prevention is preferred above early detection. Many of these factors, i.e. age and sex, can be identified preoperatively. Some of them have been included in a colon leakage score (CLS) to determine in advance whether an anastomosis or stoma should be constructed<sup>17,18</sup>. The CLS is a list of risk factors derived from a systematic search that is pre-checked before all colorectal surgeries. It contains preoperative risk factors each with a value and predicts by means of a total score the CAL-risk<sup>17</sup>. The only downside to this is that after determining a high CAL-risk, there is no possibility to change or improve the risk factors. There are pre-habilitation programs that improve the patient's preoperative status, focusing on the risk factors related to the patients' lifestyle<sup>19</sup>. Sadly the effect on reducing the risk is very disappointing.<sup>19-21</sup> There is a great deal of knowledge about risk factors, but because they are

largely non-modifiable they can only make a prediction and not help with the reduction of the leakage risk.

An optimal surgical environment proves to have a beneficial effect on the healing of the anastomosis<sup>22,23</sup>. For instance, anesthesia could possibly reveal shared risk factors in relation to anastomotic healing, perfusion and ischemia. Other changes in hemodynamic parameters during surgery can also be related to the risk of CAL. The importance of individual perioperative hemodynamic parameters during surgery on the postoperative outcome is widely described in literature. This warrants the hypothesis that optimal perioperative hemodynamic parameters are relevant on the healing of an anastomosis. Studies show that a large number of parameters are out of balance during the operation. For example, the influence of an elevated glucose in non-diabetes patients<sup>24-26</sup> or intraoperative hypotension<sup>27,28</sup> has been associated with a higher risk for postoperative adverse events. A lot of risk factors for CAL are not taken into account yet, even though there is plenty of information available that suggests further research concerning these parameters. Modifiable factors that are able to be optimized. These parameters are not currently being explicitly monitored or optimized during the operation, in particular, while making the anastomosis. Additionally, optimal values for hemodynamic parameters are even hardly established.

Due to these modifiable factors more studies are gaining interest in a multidisciplinary approach to prevent surgical complications. Since CAL has a multifactorial etiology, it can be hypothesized that intervention in modifiable risk factors might lead to a reduction of the incidence of CAL. This suggests a close collaboration of the surgical and anesthesiological team is essential, making this the first attempt to construct a tool that could reduce the patients' risk of CAL intraoperatively.

Prior to this multicenter prospective cohort study, a systematic review was performed summarizing the preceding studies on (perioperative) risk factors. The summary contains a report of these parameters, how important they are and if they show deviations during surgery. It was used to compose the checklist for the Leakage Check procedure, providing guidance on the available knowledge on this topic.

### **Leakage Check procedure**

The Leakage Check procedure will monitor possible perioperative risk factors right before the creation of the anastomosis. If perioperative risk factors are identified in the observational study, a follow up study will be done with a renewed Leakage Check procedure. The detected deviating risk factors will then be optimized to hopefully improve the healing of an anastomosis. At this moment no specific protocol exists whether to decide perioperatively to construct an anastomosis or to apply a stoma. A perioperative Leakage Check procedure will possibly create uniformity and increases awareness amongst surgeons and anesthesiologists in their approach to perform an anastomosis. Using a Leakage Check procedure, the actual performance status of the patient will be identified more securely.

The final purpose of this study is to assess reduction of CAL. Awareness to CAL throughout the entire treatment process needs to be extended.

## 2. OBJECTIVES

### **Primary Objective:**

1. Identify both relevant and modifiable perioperative risk factors of Colorectal anastomotic leakage in a Leakage Check procedure, a multifactorial checklist, right before the creation of the anastomosis.

### **Secondary Objectives:**

2. Observe deviations of the parameters in the checklist during surgery.
3. Determine the extent of these parameters as risk factors of CAL.
4. Perceiving a possible reduction of CAL due to extra emphasizing of the hemodynamic factors.
5. Creating a profile identifying high risk patients perioperatively.
6. Increasing the awareness amongst surgeons of the influence of perioperative parameter changes for CAL.

### **Study aim**

The ultimate goal is to create a follow up study with the intention to intervene or optimize those risk factors, identified by this current study, possibly leading to a reduction of CAL.

### 3. STUDY DESIGN

The Leakage Check procedure will use perioperative risk factors identified in a systematic review. The Leakage Check procedure will be developed in a format that is already accepted and applied in the operating room before the start of the operation. Preoperative risk factors will be screened prior to the operation. This will be done by using the colon leakage score<sup>17,29</sup>. Informed consent is requested prior to the operation.

The Leakage Check procedure is a multifactorial checklist that is scored with the whole surgical team prior to a surgical procedure. For this study a colorectal checklist has been designed, that will be scored during surgery prior to the creation of an anastomosis. The checklist is carried out by a member of the operation team. The checklist will also be offered through a website to minimize the registration burden in other hospitals. The checklist contains five main general topics; general condition, perfusion, contamination and visibility of the surgical field and surgery related factors. For each topic a number of parameters and inquiries are required to be answered.

This study is a multicentre observational cohort study with gradual introduction of the protocol (see Table 1) over the participating hospitals. At the moment there is participation of seventeen hospitals in the Netherlands. The reason being that there is a large group of anastomotic procedure outcomes without perioperative monitoring necessary that can be used to compare the Leakage Check procedure results with. To test the hypothesis, that even only keeping track of the risk factors a reduction of CAL occurs, a prospective group without perioperative monitoring is required as zero group. January 2016 is the starting point (T0) of the first hospital with the Leakage Check procedure, three months later the second hospital starts with implementing the Leakage Check procedure.

Table 1. Gradual introduction. **T**: number of months from start point till implementing a Leakage Check procedure . **Green columns**: Using a Leakage Check. **Red columns**: Not using a Leakage Check.

MMC T:0	
VUMC	T:3
To be determined	T:6
To be determined	T:9
To be determined	

In every participating hospital one individual has been designated to determine which patients are included. Every week scheduled patients for colorectal surgery with anastomosis will be selected by one local colorectal surgeon in the VUMC and MMC. Hopefully almost all operations with anastomosis will be enrolled in our study, since there is no difference in treatment or potential damage. This must also be communicated to one main individual in the VUMC (D.E. Huisman) to create a good overview of the scheduled Leakage Check procedure. The performing surgeon requests to apply the questionnaire at the moment before constructing the anastomosis. The anesthetist, operating room nurses and other relevant team members in the operating room (OR) will be asked to participate in this procedure. The questionnaire is found on the website [www.naadlekkage.nl](http://www.naadlekkage.nl). Every participating hospital has an own account on this website. Data following this procedure will be securely collected in a prospective online database. Patient characteristics, laboratory, pathologic, radiologic, hemodynamic and surgery related items will be scored and added. In order to obtain reliability of the results, the Leakage Check procedures that have been completed in more than 90% will only be taken into account.

Before starting with the execution of the Leakage Check procedure, the research will be announced to all predicted partici employees.

Important preoperative factors as well as postoperative complications need to be monitored. For every Leak Check patient, it is necessary to fill in a two pages' questionnaire with preoperative and postoperative outcome information. It is important that all CAL cases are diagnosed in accordance with the guidelines. It is necessary to comply with the definition of Reisinger<sup>30,31</sup> in order to be reckoned as CAL. The definition of anastomotic leakage is: "Clinically relevant anastomotic leakage was defined as extraluminal presence of contrast fluid on contrast-enhanced CT scans and/or leakage when relaparotomy was performed, requiring reintervention. Indications for CT or relaparotomy were based on clinical presentation, including fever, tachycardia, tachypnea, low saturation, low urinary production, abdominal pain, and signs of ileus or gastric retention."

Statistics are used to calculate a possible difference between patient outcomes and deviations in perioperative parameters, by means of a chi-squared test. The patients are divided into two groups, with and without CAL complication. The final purpose of this study is to optimize the risk factors in a follow up study. The determined perioperative risk factors will be ascribed optimum values by using the results of the Leak Check-Study. Dividing the patients into leaking and non-leaking groups to determine the most average values for perioperative factors. These results can be compared with the so-called optimal values from the literature of the systematic review. From these results, a new Leakage Check questionnaire will be designed for in the follow up study, containing often aberrant and modifiable perioperative factors and their optimal range. It depends on the obtained results how the optimization will take place.

### **Processing of data**

There is data collected from three different time periods:

- Preoperative data classification into complication risk.
- Leak Check data intraoperatively.
- Postoperative outcome data.

Participating health centers are offered two methods of processing the data.

## 4. STUDY POPULATION

### 4.1 Population

The intended population for this study consists of all consecutive adult patients undergoing colorectal surgery with anastomosis for benign as well as malign cause and treated at the participating centers.

The intended population for this study consists of 2000 adult patients undergoing colorectal surgery with anastomosis for benign as well as malign cause.

### 4.2 Inclusion criteria

Subjects participating in this exploratory scientific project must meet all of the following criteria:

- Subjects undergoing colorectal surgery with any kind of anastomosis.
- Can speak and understand the Dutch language.
- Is pre-operatively in good physical health as defined by ASA (American Society of Anaesthesiologists) physical status classification system 1, 2 and 3.
- Is capable of giving informed consent.

### 4.3 Exclusion criteria

- No exclusion criteria.

### 4.4 Sample size calculation

In order to ensure there will be enough patients to properly evaluate the effect of optimizing perioperative risk factors on the incidence of CAL, we performed a power analysis. This sample size was calculated using a 2-sample test of proportions with the two primary subgroups being patients with de deviating perioperative parameters and patients without deviating perioperative parameters. Calculation of an initial sample size of >2000 patients, assuming a significance level of  $\alpha = 0,05$ , to achieve a power of 80% to detect a difference of  $\delta = 0,06$  between the subgroups, assuming a 8% leak in the group with deviating risk factors and 2% in the group without deviating risk factors.

## 5. METHODS

## 5.1 Study parameters/endpoints

### 5.1.1 Main study parameter/endpoint

Main parameter is number of CAL patients with deviating perioperative risk factors.

### 5.1.2 Secondary study parameters

Secondary parameters are number of deviating risk factors in total and feasibility of scoring a checklist during surgery.

## 5.2 Leakage Check procedure

For this study a colorectal checklist has been designed, that will be scored during surgery prior to the creation of an anastomosis. The checklist is carried out digitally on [www.naadlekkage.nl](http://www.naadlekkage.nl), so it can be completed during the surgery. The checklist contains four main general topics; general condition, perfusion, contamination and visibility of the surgical field and surgery related factors. For each topic a number of parameters and inquiries are required to be answered. A systematic review was performed summarizing the preceding studies on (perioperative) risk factors. All the parameters and inquiries (see **table 2**) for the Leakage Check procedure have been found relevant factors with proven predictive values for the occurrence of an anastomotic leakage.

*Intraoperative modifiable risk factors of colorectal anastomotic leakage.*

*A systematic review of literature*

S J van Rooijen/D E Huisman/B T Bootsma/M Stuijvenberg/RMH Roumen/G D Slooter/G Kazemier/F Daams

**Table 2. Leakage Check procedure**

<u>General condition</u>	<u>Perfusion</u>	<u>Contamination and visibility</u>	<u>Surgery related factors</u>
Temperature	Blood loss		Analgesia
Glucose	O <sub>2</sub> saturation	Contamination surgical field	Surgeon Fit to perform
Antibiotics	MAP		Elective operation Anastomose
Inotropic	Subjective rate of local perfusion		Operation Intra operative event\
Door movements	Fluid balance		Stoma Hospital

### **5.3 Withdrawal of individual subjects**

Only applicable if participants decide to withdraw before surgery. The investigator can decide to withdraw a subject from the study if the patient ends up not receiving an anastomosis.

### **5.4 Premature termination of the study**

In case of insufficient funding.

## **6. STATISTICAL ANALYSIS**

### **6.1 Statistical plan**

Evaluation of relationships between parameters deviations and leakage rates of anastomosis. Analyses for outcome will be performed on the 2 groups, one with CAL and a group without CAL. Data will be analyzed with Statistical Package for the Social Sciences software version 20 (SPSS Inc., Chicago, IK, USA).

### **6.2 Publication**

All participating centres will be involved if it is decided to publish the data in question. D.Huisman is the principal investigator. She is supported in the VUmc by F. Daams and B. Bootsma. For one hundred delivered Leak Checks each center is given an authorship on the article. Each centre will also be named in the acknowledgements.

## **7. ETHICAL CONSIDERATIONS**

### **7.1 Participant's rights and privacy**

Participants will be informed about the study but they will be treated similarly. The privacy of the participants will be guaranteed as in regular clinical routing.

### **7.2 Recruitment and consent**

The data of several medical centres will be processed by the VU Medical Centre and therefore informed consent is required. The patient will be offered to participate in the study during an appointment at the polyclinic. He will receive an information letter. At the next appointment, the patient will be approached for written consent. There must be a 24-hour time period before consent is given.

### **7.3 Benefits and risks assessment, group relatedness**

#### **Participant's benefits**

Regarding the study objectives, this study can be beneficial to participating patients since extra attention is made to optimize patients' condition perioperatively.

#### **Participant's efforts**

There is no participant effort involved.

## **8. ADMINISTRATIVE ASPECTS AND PUBLICATION**

### **8.1 Handling and storage of data and documents**

To ensure confidential use of patient data, participants in this study receive a study number. This number does not include details which are derived from participant's details. The subject identification code is linked to the participant's details by the study coordinator. This link is kept digitally in the VU University Medical Center for VU patients and in the Máxima Medical Center for MMC patients, and safeguarded by a password, known by the study coordinator. Hereby, outsiders cannot relate any results or data back to the participant.

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