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Protocol version 18 further updated 20160113 before analysis of data, and changes are marked in grey.

## **EASY**

**Early closure of temporary ileostomy - A randomized controlled trial**

**Early versus late closure of temporary ileostomy after rectal resection due to rectal cancer**

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## **Project organisation:**

### **Steering group:**

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Eva Angenete, MD.

### **Project secretariate:**

Situated at Sahlgrenska University Hospital/Östra, SE-416 85 Göteborg, Sweden

### **Local investigators:**

Denmark:

Herlev Hospital: Anne Kjærgaard Danielsen, PhD

Sweden:

Göteborg: Adiola Correra, PhD student

A local investigator will be appointed to be responsible at each participating hospital.

### **Publication strategy:**

Both positive and negative results will be published in internationally recognized journals. If publication in that type of journal is not possible the results will be published on the home page of the research group.

Co-authors according to criteria from the Vancouver group ([www.icmje.org](http://www.icmje.org)).

### **Data reporting**

Data will be reported locally in Case Report Forms (CRF), which accurately contain the relevant details necessary to evaluate the questions of the study (CRF attached as appendix 8)

The original CRF's will be archived locally in accordance with current regulations.

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**Randomisation**

Patients will be randomized in blocks of 6 from a computer generated list and the necessary number of numbered envelopes will be sent out to participating departments together with CRF for data reporting.

***Participating centers:***

The study takes place within the framework of the Scandinavian Surgical Outcomes Research Group (SSORG) and it is expected that the Swedish and Danish surgical departments that are members of the network will participate. There is also the possibility that other surgical departments in Denmark or Sweden may participate.

**Denmark:**

Herlev Hospital, University of Copenhagen

Nordsjællands Hospital, University of Copenhagen

**Sverige:**

Sahlgrenska University Hospital

NÄL, Norra Älvsborgs Sjukhus

Skaraborgs Sjukhus, Skövde

## Flowchart

Patients with temporary ileostomy after surgery for rectal cancer

CT-scan 6-8 days after stoma construction

Inclusion

Randomisation

Control group

Intervention group

Investigation of complications before discharge

Closure of ileostomy 8-13 days after stoma construction

Investigation of complications before discharge

3 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36, OAS + EORTC QLQ-CR30/29)

3 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36 + EORTC QLQ-CR30/29)

Closure of ileostomy min. 12 weeks after stoma construction

6 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36, OAS + EORTC QLQ-CR30/29)

6 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36 + EORTC QLQ-CR30/29)

12 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36, OAS + EORTC QLQ-CR30/29)

12 months (+/- 2 weeks) after stoma construction

- Investigation of complications
- Quality of Life assessment (SF-36 + EORTC QLQ-CR30/29)

Cost calculation

Cost calculation

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## Background:

To have a stoma is not one single condition, but is defined by the fact that there are many types of stoma, many underlying reasons for the stoma and many individual psycho-social factors, which naturally affect people differently (1-4). Patients have to adapt to a different body image (how one views one's body), changed daily routines and for some it will also result in changes to life style, social activity (5) and affect sexuality (6). At the same time the construction of a stoma is also a treatment which eliminates illness, ameliorates pain and prepares for wellness (7), in which case stoma construction can also have a positive meaning (8). The importance of the stoma construction can also be pushed into the background due to other associated processes, e.g. parenteral nutrition (9), complications (10), fecal incontinence (11) and cancer (12). Many factors influence even the simplest adaption to life with a stoma, such as age (13), socio-economic status (14) and gender (15). The stoma construction itself can be associated with complications and can be of a type that in the long term will affect quality of life (10, 16-18).

Patients who are admitted for surgical treatment of rectal cancer are in some cases offered a low anastomosis with simultaneous construction of temporary ileostomy for relief of rectal anastomosis. The temporary ileostomy prevents complications in the form of anastomosis leakage requiring surgery, but on the other hand, not anastomosis leakage in general (19).

Several preliminary studies, however, indicate that the frequency of complications can be reduced for selected patients by closing a temporary stoma within two weeks (20). There is usually low mortality in connection with the closure of temporary ileostomies, regardless of the timing of the closure (20). Though one retrospective study has a noticeably high mortality of 1% and 5.3 % for respectively colostomy and temporary ileostomy (21) where the deaths were connected with anastomosis leakage, sepsis, acute myocardial infarction and one death for unknown reasons.

Stoma construction can result in complications which require re-operation and one study concluded that there is a great variation from no cases up to 14%-17%, where only the presence of inflammatory bowel disease is a particular risk factor (20).

One prospective study showed that earlier closure of stoma (11 days rather than 2-3 months) was not associated with increased morbidity or mortality (22). A retrospective study including 308 patients who received a temporary loop ileostomy and subsequently underwent

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closure found a positive correlation between creation of a loop ileostomy and a reduced renal function (23).

A smaller randomized study examined the importance of early closure (9 days after operation) of ileostomy in 36 patients selected pre-operatively. This shows that hospitalization (overall) was significantly shorter and that bowel function and resumption of oral nutrition was not a problem and concludes that with the study's controlled design in mind there was no increased risk associated with early closure of the ileostomy (24).

A randomized and controlled study of 190 patients where the intervention group had their stoma closed after 8 days against the control group, whose stoma was closed after 60 days, showed no significant difference in the number of complications though there was an increase in the time spent in hospital for the group with later closure. There were significant differences in the type of complications in that the incidence of wound complications in the first group was greater, but in the second group there were more patients with obstruction of the small intestine and medical complications (25).

Quality of Life assessments are increasingly required in the health sector (26;27), and it is common to measure the effects of interventions on patients' quality of life (29). Therefore it seems obvious to examine the impact on patients when a temporary ileostomy is closed and a survey of 76 patients with temporary stoma found that more than half of them felt socially impacted by the stoma, and 12% were completely isolated (5). A prospective study over five years of rectal cancer showed that stoma construction generally decreases quality of life and closure of stoma brings improved quality of life (29).

The pressure on the health sector is increasing, resulting in the need to use other tools than the strictly academically orientated, and economic prioritizing of treatment and nursing care for different patient groups (30). Thus a cost analysis can be used to support professional decisions when new treatments and methods are introduced into the health sector (31).

### ***The purpose of the study:***

This study will analyze differences between two different surgical operative regimes in connection with the closure of a protective temporary ileostomy after treatment for rectal cancer. The difference between the two regimes is the interval between constructing the ileostomy (the first operation) and the closure of the stoma (the second operation). The interval until the ileostomy is

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closed will be 8 – 13 days for the intervention group, and 12 weeks for the control group, which corresponds to normal clinical practice.

Differences identified in relation to the frequency and nature of postoperative complications, mortality, the health economic effect and the health related quality of life for the patients.

***Hypotheses:***

Primary:

- Patients who have an ileostomy closed on day 8 – 13 have fewer complications than patients who have the stoma closed after minimum 12 weeks.

Secondary:

- Cost effectiveness analysis shows that early closure of ileostomy is cost effective in comparison to late closure.
- Patients with early re-establishment of normal gastrointestinal function (8-13 days post-operatively) will have better health related quality of life in comparison with patients whose gastrointestinal function is re-established after a minimum of 12 weeks.
- Patients in the control group will have a significant reduction of renal function compared to the intervention group.

***Endpoints:***

Primary:

- Mean number of complications per patient after index-operation and up to 12 months after (covering any complication including stoma related complications).

Secondary endpoints:

- Percentage of patients with at least one complication with Clavien-Dindo Classification of Surgical Complications (34;35) severity grade IIIA, IIIB, IVA, IVB or V after index-operation and up to 12 months after.
- Mean number of stoma-related complications after index-operation and up to 12 months after. Supporting endpoint is Comprehensive complication index (CCI) after index-operation and up to 12 months after.

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- Analysis and comparison of creatinine levels at both index surgery and prior to loop ileostomy creation.
  - Analysis and comparison of health related quality of life as measured with SF36 3, 6 and 12 months after stoma construction.
  - Analysis and description of quality of life specific to the illness measured with EORTC QLQ-CR29 three, six and twelve months after stoma construction if stoma not closed.
  - Analysis and description of quality of life specific to the illness in the control group measured with Ostomy Adjustment Scale 3, 6 and 12 months after stoma construction if stoma not closed.
  - Recording and comparison of the total costs for the control and intervention groups respectively 0-12 months post-operatively.

## **Design:**

The study will be carried out as a prospective randomized controlled multi-center study of patients, who have temporary ileostomy due to rectal cancer in Denmark and Sweden.

The primary and secondary outcomes of the study will be evaluated at all participating centers.

## **Selection:**

After ileostomy construction patients will be included in the study (see inclusion criteria). Patients will be randomized into the health intervention group where stoma is closed after 8 – 13 days or into the control group where stoma is closed after minimum 12 weeks. Both groups will be examined for post-operative complications at discharge and at 3, 6 and 12 months after ileostomy construction.

Additionally the effect on the patients' health-related quality of life will be examined 3, 6 and 12 months after the ileostomy construction.

Finally the health economic costs in both groups will be measured and the difference calculated.

The final report and analysis of all endpoints will be carried out after 12 months,

## **Inclusion criteria:**

Adult mentally competent patients who have been operated for rectal cancer with construction of protective temporary ileostomy can be included in the study.

The first days after the operation the patient is assessed by a doctor and it is decided if the patient is suitable for inclusion. In order to be included in the study the patient must not show signs of active

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infection or organ failure. Patients must not show signs of anastomosis leakage. This is ensured by testing for radiological signs of anastomosis leakage with a contrast CT scanning or a flexible endoscopy of the anastomosis which will be a standard part of the department during the course of the project. Additionally the patients will have a functioning stoma (both feces and flatus).

Patients are included on the basis of professional assessment by experienced colorectal surgeons and the patients' post-operative recovery is documented as data describing degrees of post-operative status. This includes: CRP, red blood cells, nutrition, mobilization and stoma function:

When the patient is considered suitable for inclusion the patient is informed verbally and in writing and the patient's written consent is documented before the patient is included (see section on consent).

Patients will be included 6-11 days after the operation while they are admitted to the ward. Patients are randomized 6 – 11 days post-operatively to be included in the control or the intervention group.

**Exclusion criteria:**

- Patients on steroids
- Patients with diabetes
- Patients with speech problems
- Patients with anticipated poor compliance ie for psychiatric reasons.

**Exclusion:**

Patients who withdraw their consent to participate

**Stopping the study:**

There are no predictable reasons why the study should be terminated.

**Sample size**

**The calculation of the primary endpoint: Morbidity and mortality**

*Sample size*

The study protocol specified 72 evaluable patients per group to have 80% power to detect a 66% reduction in the risk of complications<sup>12</sup>. Due to slow enrollment fewer evaluable patients were reached and before data analysis we did a recalculation. With the current primary endpoint, 60 evaluable patients per group would have 80% power to detect a 62.5% reduction in the annual mean

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rate of complications using a two-sided test with 5% significance level and assuming a mean rate of 0.45 in the control group.

### **Registration of included patients:**

We will ensure that all patients who meet the inclusion criteria in practice are included which will be evidenced by the screening log, where non-included patients as well as patients who leave the study will be identified.

Patients who after inclusion wish to exit the study will be asked if data already collected can be used in the study or if it should be deleted. Data will be treated according to the patients' decision.

## **Methodology:**

### **Morbidity:**

The primary endpoint for the study is the rate of post-operative complications up to 12 months after surgery.

The data form is developed based on the Clavien-Dindo Classification of Surgical Complications (C-DCSC)(34;35). C-DCSC is used to ensure that data is collected by objective criteria to minimize the influence of personal and/or cultural bias.

The basic concept for the form is to classify complications after treatment and in doing so avoiding individual and ambiguous evaluations such as "severe" or "less severe" complications.

All complications will be recorded according to type or degree, ie a form for each complication treated will be completed. Stoma related complications will be registered according to symptoms from the stoma and/or the surrounding skin.

The classification includes all complications (including stoma related complications) that occur during the six months that the investigation is progressing (34), ie immediately before discharge and 3, 6 and 12 months after construction of ileostomy.

### **Cost calculation:**

Only the most significant costs will be included in the project, including outpatient contacts for stoma clinics and surgeons as well as individual health benefits associated with municipalities and the private sector.

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Calculation of costs will be made based on recorded admission days, including readmissions, outpatient tests / interviews and reoperations. In addition, questions are asked about demographic data such as level of education and income. The patients' use of services from GPs and community health care and possible return to work will be recorded. It will either record the costs associated with the use of medical services by their GP or nurse, or relate to the reduction of social costs if patients move from being unwell to being part of the working population (36, 37). Social activities and possible return to the workplace will also be recorded, as it indicates that patients have resumed a normal life.

The records rely on self-recording in a diary which will be given to patients on discharge, as this kind of information can be difficult to access retrospectively, when patients are likely to forget or overlook visits (38;39). The use of a diary for recording data in combination with cost calculation is a valid method of capturing events that either happen outside the admission period or occur in a patient's daily life.

### **Health related quality of life:**

The project also intends to assess and compare the health related quality of life with Short Form 36 (SF36) 3, 6 and 12 months post-operatively. In addition we will assess the illness specific quality of life in the form of European Organization for Research and Treatment of Cancer QLQ-CR30+CR29 (EORTC QLQ-CR30+CR29). Further we will assess and describe the stoma specific quality of life in the control group by use of the Ostomy Adjustment Scale (OAS).

Short Form 36 (SF36, general quality of life)(40) EORTC QLQ-CR29(41;42) and Ostomy Adjustment Scale (OAS, illness specific quality of life ) (43;44) are all constructed as easily accessible questionnaires designed to be completed in the presence of an interviewer, self-completed or completed by telephone. Additionally patients are asked about demographic data about education, work and marital status.

SF-36 was developed in an American study for assessing general health concepts and the form has since been used in many clinical and population studies and has been validated in international and Danish and Swedish studies. SF-36 is a questionnaire which can be used to evaluate people's general health status by completion either by the individual or by an interviewer. It only takes 15-20 minutes to complete. The questionnaire can be used to assess generic measure of health status which means that it can be used for all age groups (from 14 years upwards) and for all patient groups. The questionnaire assesses the person's general health status partly via self-evaluated health

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questions and partly by questions that assess physical, social and psychological functions. The questionnaire consists of 36 questions which are divided into 8 scales, where half consolidate into a summary measure of physical health and the other half in a summary measure of mental health to give an assessment of the person's overall health

EORTC QLQ-CR 30 + CR29(41;42) was originally developed in 1987 as a cancer specific assessment tool under the leadership of EORTC (CR30), which is an international non-profit organisation. The present version of CR29 has been edited and contains a general cancer specific part (CR30) and a more specific part for gastrointestinal symptoms (CR-29), for practical purposes the two questionnaires are always used together. They contain a total of 59 questions which make up functional scales, symptom-oriented scales and a quality of life scale.

OAS is a questionnaire which was developed to evaluate patients' subjective adaption to life with stoma focusing on physical, psychological and social changes following stoma construction.

There are 34 questions answered on the Likert scale from 1-6. This gives a possible outcome of 34 to 204 points, where the higher score indicates better adaption and consequently a higher health related quality of life. The table is validated and used for patients with different stoma and can be used at various points of time in the context of stoma construction.

Both general and illness specific quality of life is assessed at 3 months (+/- 2 weeks), 6 months (+/- 2 weeks) and 12 months (+/- 2 weeks) after construction of a temporary stoma. It is presumed that at the time of the first assessment at 3 months patients in the control group have not undergone stoma closure. The questionnaire is aimed to be used for patients only while they still have a stoma. The assessment will be completed by the patient in the presence of an interviewer to ensure a high response rate and to minimize problems with comprehension.

### **Closure of ileostomy:**

Carried out after satisfactory examination and evaluation of

1. anastomosis density by contrast CT scan or a flexible endoscopy of the anastomosis
2. whether the patient has a current infection
3. the general health of the patients, as set out in a specific form for post-operative recovery.

Ad 1. The patient will undergo a localized low radiation CT scan (blank scan) with 5% dilute aqueous contrast in the rectum. Immediately before the examination radiologist, a specially trained registered nurse, or a surgeon (according to local protocol) will insert a Foley catheter (a short tube made of flexible plastic) into the rectum of the patient and inject 300-400 ml aqueous contrast in 5% solution. This makes it possible to observe the anastomosis and evaluate the seal. For the duration of the project CT scanning after rectal surgery will be standard and will take place 6-8 days post-operatively and be evaluated by a surgical or radiology specialist. Alternatively, centers may decide to examine the rectum performing a flexible endoscopy of the anastomosis.

Ad 2. Post-operatively patients will have daily blood samples taken according to the department's protocol, including creatinine levels.

Ad 3. The general condition of patients will be evaluated by a surgeon and documented in the form in CRF:

| <b>Postoperative recovery</b> |  |                                   |
|-------------------------------|--|-----------------------------------|
| CRP (value recorded) _____    |  | Hæmoglobin (value recorded) _____ |
| Nutrition (please tick)       | Patient eats and drinks sufficiently     |                                   |
|                               | Patient needs i/v fluids                 |                                   |
|                               | Patient needs total parenteral nutrition |                                   |
|                               | Patient needs gavage                     |                                   |
| Mobilising (please tick)      | Patient gets up >6 times/day             |                                   |
|                               | Patient gets up <6 times/day             |                                   |
|                               | Patient gets up <1 time/day              |                                   |
| Stoma function (please tick)  | Faeces _____                             | Flatus _____                      |

**Timing of closure operation:**

Intervention group:

Closure of the ileostomy will take place 8 – 13 days postoperatively and will follow the usual protocol for the department, including in regard to hand stitching or stapling.

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Control group:

Closure will take place after minimum 12 weeks and will follow the usual protocol for the department.

**Stoma training in the control group:**

Patients will receive the departments' usual training to enable them to do their own stoma care until the stoma is closed. This means that patients are assigned to the stoma clinic and will be trained by the department staff and stoma nurses as required.

**Stoma training in the intervention group:**

Patients will receive the usual stoma training after inclusion and until randomization. Thereafter it will not be necessary for them to go through the full training schedule. The training will be aimed at completely individual needs such as going home on leave for a couple of days. It may, for example, focus on learning how to empty the bag, switch plate and observing the bag. The patient may want go home on leave a couple of days before the second operation, which will depend on individual conditions.

**Ethical aspects of the study:**

Participation in the study is voluntary and happens after verbal and written information to patients in accordance with ethical requirements in Denmark and Sweden. The study will be carried out in accordance with the Helsinki II declaration and law 503 from 1992 covering scientific committee systems and will wait for approval from the local Ethical Committee before starting. The operations will be carried out in surgical departments which specialize in colorectal surgery and where closure of temporary ileostomies and other treatment procedures are part of the standard regimes at the department. Thus it will only be the timing of the closure of the temporary ileostomy that is not part of the routine. Each participant is free to withdraw from the study without affecting the observations, treatment or nursing of the patient. The authorized health personnel involved in the project will demonstrate professional care.

***Risks and side effects of the study:***

The actual operation is the same for the intervention and control groups, the control group undergoing surgery according to current and usual local guidelines. The intervention group receives exactly the same treatment and follow-up and nursing care as the control group, other than the

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stoma training, which of course will be individually tailored to the fact that the patient will not need to live with stoma.

As we have mentioned, previously published studies do not indicate that there is an increased risk associated with earlier closure of temporary ileostomy provided that the patient has been examined and assessed for this by the surgeon.

There are no known risks or side effects connected with completing the questionnaire. It is expected that patients will experience a great improvement of quality of life in connection with earlier return to normal bowel function. It is also expected that patients will be able to return sooner to general activities, such as sport, work and other social and personal activities, including a normal family life. The study will contribute to final recommendations for the timing of closure of temporary ileostomies in relation to morbidity. This will be of importance for future development of clinical guidelines in this area. The study will also contribute new health-economic knowledge used for rankings and comparisons in health care. Additionally the research will provide knowledge of how quality of life is affected during the course of temporary ileostomy, which is of importance for clinical nursing care and treatment.

### ***Scientific approval:***

The project is approved by the Science Ethical Committee for the capital region in Denmark. In Sweden the project will be approved in the same manner by the Ethical Approval committee in Göteborg.

### ***Approval of data security:***

The project is approved by the Data Protection, Denmark and by the Personal Data Representative at the Sahlgrenska University Hospital, Västra Götaland Region in Sverige

### ***Clinical Trials:***

The project is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) by the principal investigator.

### ***Financial support:***

There is no financial support from commercial sources.

If the project achieves financial support the money will be paid via a research account administered by Herlev Hospital.

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If the project does not get financial support, money will be found from the department budgets, as it is mainly about re-scheduling existing treatments. The project was initiated by the principal investigator Jacob Rosenberg, Professor, senior surgeon, MD who is employed and paid by Herlev Hospital. Anne Kjærgaard Danielsen, PhD, RN and also employed and paid by Herlev Hospital.

***Remuneration for participating patients:***

Patients will not receive payment for their participation.

**Guidelines for collection of informed consent:**

Patients intended for inclusion will be informed verbally and in writing by the local investigator.

When patients have agreed to participate and have signed the consent agreement they are included in the study. Patients are randomized into the control or intervention groups after inclusion.

Information about the study will happen immediately after the inclusion of the patient ie after CT scan and assessment by a doctor. The written material will be given to the patients to read after the patient has been informed verbally. The verbal information conversation will be held in an undisturbed place or an interview room, or if the patient is confined to bed by making sure that the patient agrees to be informed in the ward. Any other patients in the ward will be asked to leave the ward if this is possible. The patient will be encouraged to have a support person present during the information and the arrival of this person will be awaited. The written material will be delivered by a health care worker who has been appointed by the responsible local investigator. The verbal information will be handled by a health care worker who has been appointed by the local investigator and who is competent to answer the questions that might arise from the patient or the support person.

After patients have been informed they have 24 hours to consider giving consent to participate, but they can withdraw their consent at any stage of the study.

Inclusion in the project happens after the patient has given written and verbal agreement to participate in the study. Patients will be randomized to the control or intervention groups when they are included in the project. Independently of the randomization the patients will be informed about the operation according to the usual procedure in the department.

**Timeline for the project**

Start February 2011

Inclusion of patients February 2011 – November 2014

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Reporting of morbidity until December 2015

Analyses of data and writing up results February 2016

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