

# **Surviving Rectal Cancer at the Cost of a Colostomy Quality of Life, Socioeconomic Factors and Colostomy Impact in an International Perspective**

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## **Protocol for the International validation of the Colostomy Impact Score**

April 24<sup>th</sup> 2018

NCT number: n/a

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**Background:**

Stoma formation may be necessary after bowel surgery and involves diversion of the bowel to the skin, where the gut contents are emptied into a bag. Data from Denmark and the UK indicates that, in Northern Europe, 2 000 per 1 million people are presently living with a stoma <sup>1</sup>. In the treatment of rectal cancer, low anterior resection (LAR) with sphincter-preserving surgery following the principles of total mesorectal excision (TME), is the current gold-standard treatment. In cases where the tumour threatens the sphincteric apparatus, an abdomino-perineal excision (APE) is performed. Hartmann's procedure is chosen in a selected group of patients in whom an attempted primary anastomosis is not safe or technically feasible. An APE and many Hartmann's procedures will result in a permanent end colostomy <sup>2-4</sup>

The change of anatomy can cause practical difficulties and can cause a feeling of loss of control and changed body image. It is well-established that these changes can reduce the patients' quality of life and have negative impact on daily living<sup>5-9</sup>. Studies have also shown that living with and the acceptance of a stoma have large cultural, social, religious, and demographic differences. Likewise, how Health Related Quality of Life (HRQoL) is perceived may differ between various populations<sup>10,11</sup>.

With an increasing population of cancer survivors, there is a need for attention towards the long-term sequela appearing when patients are adjusting to a cancer free life in their own homes. The negative impact on bowel function after surgery for rectal cancer with an anastomosis the LAR-syndrome has been meticulously studied recent years with great benefit for patients specially with the development of the LARS-score<sup>12-14</sup>. To make the same progress with stoma patients there is a need for a quick and reliable quantification of stoma-bother, identifying the patients with poor functional results in need of further attention and treatment.

Recently, we have developed 'The Colostomy Impact Score' (CI-score), which is a simple scoring system evaluating stoma-problems in patients with a permanent colostomy after rectal cancer surgery<sup>1</sup>. It was based on direct patient-reported individual outcome measures concerned with various aspects of daily life with stoma, as mapped against overall HRQoL. 610 patients treated between 2001-2007, answered a 22-items basic stoma questionnaire and one anchor question addressing the overall stoma impact on HRQoL. Regression analyses identified 7 items/questions with significant impact on HRQoL, and each item/question was allocated a weighed scoring-value. The score comprises 7 items and has a sensitivity of 85,7% for detecting patients with significant impact on HRQoL.

This CI-score is currently available in Danish and English and was developed on a Danish population. We believe it to be a quick and reliable tool to screen patients for stoma-related negative impact on HRQoL. There is no doubt that there are significant cultural, social, religious, and demographic factors that can influence a patient's experience of life with a stoma. In addition to this, perception of an individual's HRQoL is known to differ between various populations [13], [14]. Therefore, before widespread uptake of the CI-score can be promulgated, studies on reliability and validity must be performed internationally across multiple patient populations.

This retrospective cohort study has three main aims: 1) To identify demographic and socioeconomic factors influencing stoma impact and HRQoL, 2) To assess reliability and to validate the translated and cross-cultural adapted CI score internationally in multiple different centres, across a variety of patient groups and across cultural, religious, socioeconomic and physical borders and 3) To investigate if differences in everyday stoma care and -costs across countries and cultures affect CI or HRQoL.

### **International validation of the Colostomy Impact Score**

**Objectives:** To study the influence of diversity in demographic, religious and socioeconomic factors as well as everyday stoma care on CI-score and HRQoL between countries and cultures.

Furthermore, to study the reliability and validity of the CI-score in different countries (Australia, Brazil, China, Denmark, Egypt, Israel, The Netherlands, Lithuania, Portugal, Russia, South Africa, Spain, Sweden, Turkey and the UK) by testing the CI-score against validated measures of quality of life and including test-retest reliability.

#### **Material and methods:**

International validation will be conducted as a retrospective cohort study. Local health care professionals will identify includable patients and register relevant clinical information on each patient from the hospital chart. Most centres will include patients from national or regional databases, some will however include conveniently if a database is not available. Our international collaborators will be responsible for sending out and collecting the questionnaires and returning the completed questionnaires to the undersigned. In countries with sufficient internet accessibility and -infrastructure the data collection will be web based i.e. patients are sent a link to the redcap-database for them to enter their answers directly. Some centres will employ paper versions of the questionnaires. In areas with substantial number of illiterates investigator led interviews can be performed.

**Inclusion criteria:** Patients who were operated with curative intent for rectal cancer with APE, Hartmann's procedure or pelvic exenteration will be included retrospectively aiming at 250 patients from each of the participating countries. This number is based on a calculation of strength based on the results from the development of the CI-score. (mean EORTC score in the major CI-group: 72. SD: 22. Minimal clinical difference: 10 points. Alpha: 0,05 STATA => sample size 206 patients. Expected dropout: 20%). Accessibility to cohorts of interest may differ between countries. Therefore, number of patients and mode of contact to patients should be agreed by the local investigation and the steering group in the planning of the data collection and included as individual amendment to the final protocol. In Denmark patients operated from January 1<sup>st</sup> 2001 to December 31<sup>st</sup> 2016 will be included.

**Exclusion criteria:** Age less than 18 years, known disseminated or recurrent disease, mental dementia and the inability to understand the actual language.

As the CI-score is a construct based on a formative model, statistical analysis based on the Classical

Test Theory (CCT) and Item Response Theory (IRT) cannot be applied. However, the following aspects of validity and reliability from the COSMIN checklist<sup>15-17</sup> can and will be evaluated:

*Content validity:* Comprehensiveness and relevance of the questions in the CI-score have been ensured with the way of the development of the CI-score with the starting point in a Basic Stoma Questionnaire developed by an expert group supplemented by patients ensuring that all possible factors affecting stoma function/impact was included before regression analysis lead to the seven weighed questions<sup>1</sup>. After translation and cross-cultural adaptation face-validity of each translated CI-score will be assessed again by the collaborators before inclusion of patients.

*Construct validity:* This will be tested with hypothesis-testing. The following a priori formulated hypotheses on the construct validity will be tested:

- With a cut-off at 10 point the CI-score will have a sensitivity of at least 85% and a specificity of at least 50% of identifying patients with substantial colostomy impact as measured by the anchor questions (Anchor 1: poor/very poor satisfaction, remaining: Some/major impact).<sup>1</sup>
- Patients with a CI-score of  $\geq 10$  have significant higher scores than patients with CI-score of  $< 10$  on all scales on the EORTC-QLQ-C30 questionnaire and this difference is clinically relevant in global health status, role functioning, social functioning and fatigue.<sup>1</sup>
- Patients with a CI-score of  $\geq 10$  have significant higher scores than patients with CI-score of  $< 10$  on all scales on the EORTC-QLQ-CR29 and this difference is clinically relevant in stoma care problems.
- Patients with a CI-score of  $\geq 10$  have significant worse index value in the EQ-5D-L compared to patients with a CI-score of  $< 10$ . The sensitivity and specificity are expected to be comparable to when comparing to the anchor questions (hypothesis #1).
- The sensitivity and specificity are expected to be the same across all countries performing the validation.
- Men and women have the same relation between CI-score and HRQoL.
- If stoma care products confer a financial burden on the household the CI-score will show poorer correlation with HRQoL compared to patients where stoma care products do not confer a financial burden on the household.
- If the patients' religious affiliation or practice conflicts with having a colostomy, the CI-score will have a poorer correlation to HRQoL compared to patients who are not religious or if their religious practice does not conflict with having a stoma.
- Patients who had their colostomy in the acute setting will have a poorer correlation between CI-score and HRQoL compared to patients operated in an elective setting.
- Patients who postoperatively had serious complication to their surgery (Clavien-Dindo  $\geq$  IIIb) will have a poorer correlation between CI-score and HRQoL compared to patients with no or minor complications.<sup>18</sup>
- The following hypotheses on differences in HRQoL between different groups will be tested:
- Women colostomates have inferior HRQoL than men
- Obese patients ( $BMI \geq 30 \text{ kg/m}^2$ ) have inferior HRQoL than patients with a  $BMI < 30 \text{ kg/m}^2$
- Patients who perform their everyday stoma care themselves have a better HRQoL than patients who require help.
- Patients using irrigation for their stoma care have a better HRQoL than patients who do not irrigate.
- Patients who report the costs for stoma care products confer a burden on their household finances have an inferior HRQoL than patients who do not report this.

- Patients who report having the possibility to see a stoma care nurse if necessary have better HRQoL compared to patients who report not having this possibility.
- Patients who have had surgery in relation to their stoma for any reason have inferior HRQoL than patients who have not have surgery to their colostomy.
- Patients who report having a bulge in relation to their colostomy have inferior HRQoL than patients who do not report having a bulge.
- Patients who believe they have a hernia in relation to their colostomy have inferior HRQoL than patients who do not report having a hernia.

For convergent validation the CI-score will be tested against 5 anchor questions (not validated) and the EORTC QLQ C30+CR29 (validated). Cross-cultural validity: See translation section.

*Reliability:* For a randomly selected subgroup in each country the CI-score and anchor question will be administered twice with an interval of approximately 2 weeks. The two administrations will be independent and both the setting when answering and the forms of administration will be similar for the individual patient. For ensuring stable patients an extra question on recent changes in stoma function will be added to the retest.

#### Translation:

Translation of the CI-score will be managed by the lead institution with few exceptions (Turkey, Russia, Israel) and will follow the translation procedure recommended by the World Health Organization. All translations are produced by a forward–backward procedure. The latter procedure is performed to ensure, that the original meaning of the concepts is derived. The original Danish version of the CI-score has already undergone a professional translation to English. A professional translation agency will perform the translation of the English version to languages in the included countries. All questionnaires/Case Report Forms (CRF) to be filled in by patients will undergo the same translation procedure as above.

The EORTC questionnaires are available in all languages relevant to this study.

#### Data management:

A master version of the questionnaires will be collected into a booklet. On this basis, a RedCap database will be constructed to allow for direct electronic data entry by patients. Patient not able to access the web-based system, will fill in a paper version of the booklet. According to variation between populations in respect to practically illiterate's investigator lead data collection will be allowed. However, this should be agreed by the local investigation and the steering group in the planning of the data collection and included as individual amendment to the final protocol.

#### Data analysis:

Construct validity: Convergent validity will be studied by testing the CI-score on APE/Hartmann-patients against two measures of HRQoL; the anchor-questions assessing the overall stoma-impact on HRQoL, the EORTC QLQ C30 questionnaire version 3.0 and the EORTC QLQ CR29. Construct validity will furthermore be assessed by hypothesis-testing assessing the direction and magnitude of the expected correlations. Test-retest reliability will be studied on a subgroup in all included

countries. Also, we will include questions on background demographics, socioeconomic status, everyday stoma care and -costs thereby enabling investigation of the practical and economic aspect of living with a stoma varying from country to country.

#### Statistical analysis:

Statistical analysis will be performed separately for each country.

The correlations between total CI-score, anchor questions and the EORTC questionnaire results will be calculated for all participating patients according to the guidelines for the scores. For each CI-score group (minor CI/major CI) the mean EORTC QLQ C30-score will be calculated, testing the overall difference of impact on HRQoL between the CI-score groups.

Using the anchor-questions, the patients are divided into two HRQoL groups of those reporting no/minor or some/major impact on HRQoL. Relationship between CI-score and HRQoL group will be illustrated in box-plot for each country, where we expect statistically significant differences in median CI-score between the two HRQoL groups. Differences will be tested by Mann-Whitney U test. A contingency 2 by 2 table will be used to assess the degree of agreement between the two CI-score groups and the two HRQoL groups. Based on this, the sensitivity for the score will be calculated for each country. The added questions about irrigation and stoma-bag change frequency will be compared country-wise. Univariate regression analysis, descriptive analysis and estimation of impact on HRQoL will be performed. Test-retest reliability will be evaluated using Intraclass Correlation Coefficient and Cohens' Kappa.

#### Ethical considerations:

Approvals will be obtained from all local ethics committees. All information collected will remain confidential. A study number will identify patients. Patients will remain anonymous for data analysis and no patients will be identifiable from the results. Data retained in the study archives will be destroyed in compliance with data protection law, as dictated by each country's regulatory requirements. Our international collaborators are responsible for applying for the necessary approvals from their local authorities. Participation provides no risk for the patients' physical or psychological health. Participation is voluntary and patients' willingness to participate will have no consequence for their future treatment and control in the departments.

#### Organisation:

This project will outgo from the Research Unit, Department of Surgery, Aarhus University Hospital. Within recent years we have achieved profound experience with patient reported outcome measures (PROMs). Recently, a multidisciplinary clinic for cancer survivorship and late sequelae to cancer treatment has been established in relation to the Pelvic Floor Unit, Aarhus University Hospital. We have established cooperation with colleagues in the countries mentioned and we have written consent that they will assist us in retrieving data on retrospective cohorts in their respective countries as described above. To support the data collection and project logistics, each collaborating site (excluding Australia, Brazil, China, Egypt, Israel and Turkey) will receive a site visit

form the lead centre in the initial project phase.

Primary publications on validation of the CI-score will outgo from the Research Unit, Dept. of surgery, Aarhus University Hospital in accordance with the following authors' agreement:

The international validation of the CI-score is a collaboration of researchers from 15 countries worldwide and to carry out the project more than one collaborator is needed in most countries. This compiles to a comprehensive list of names. Therefore, the output from the primary validation study as stated in this protocol will be published under the authorship of Helle Ø Kristensen, Anne Thyø, Katrine Emmertsen, Neil Smart, Thomas Pinkney, Peter Christensen and the "International Collaborative Group for the Colostomy Impact Score Validation". All collaborators will be registered as authors and be PubMed searchable and citable.

It is expected that the collected data will produce ideas and new research questions might emerge from the data itself. The local collaborators are encouraged formulate new research questions and protocols regarding their national cohorts. In agreement with the steering group, such research can be published with a local investigator as first author and member(s) of the steering group as co-authors in accordance with individual agreements.

#### **Funding:**

The project has received partly funding from The Institute for Clinical Medicine, Aarhus University, and a grant from the A.P. Møller Foundation for the Advancement of Medical science. Further applications for external grants are ongoing.

#### **Timeframe:**

When the study protocol has been approved by all international collaborators, ethical approvals from local ethical committees will be attained. This is expected during 2017 and collection of data will set off in the second half of 2017. We expect to receive the data over the following months and to be able to analyse the data during 2018 and publish the results by the end of 2018.

#### **Perspectives:**

The development of a quick and easy-to-use tool for assessing stoma impact on HRQoL, will improve the chances of identifying those patients severely affected by stoma-bother needing further diagnosis and treatment. If the CI-score performs successfully in different countries and cultures, we can promote research in new treatment strategies for stoma-bother internationally, hopefully improving treatment and quality of life for this group of patients.

We expect the CI-score to have high value in clinical practice and research and gain international reach. Therefore, it is mandatory that the score is translated, cross-culturally adapted and that validity and reliability of the score are investigated and documented.

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