

CLOSE-IT study

CLOSurE of Ileostomy Timing Study

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Study Protocol 1.3

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Abbreviations

ACPGBI	Association of Coloproctology of UK and Ireland
AR	Anterior Resection
CRC	Colorectal Cancer
CRF	Case Report Form
LARS	Low Anterior Resection Syndrome
QoL	Quality of Life
REDCap	Research Design and Conduct Service
UHW	University Hospital of Wales

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Abstract

Aims

A defunctioning ileostomy is often formed during rectal cancer surgery to reduce potentially fatal sequelae of anastomotic leak. Many patients suffer poor bowel function, i.e. low anterior resection syndrome (LARS), once their ileostomy is closed and delay to closure can increase incidence of LARS and significantly reduce quality of life. Despite this, time to closure of ileostomy is not subject to national targets within the NHS and delay to closure exceeds 18 months in a third of patients with a temporary ileostomy.

Clinical factors, surgeon and patient preference or service pressures may all impact time to closure yet to date no study has investigated this. The aim of this UK-wide study is to assess time to ileostomy closure and identify reasons for delays. Results will inform consensus guidelines on optimum treatment pathways following temporary ileostomy formation.

Methods

We will undertake a prospective snapshot audit together with retrospective analysis of ileostomy closure through collaboration with Dukes' club members and the National Research Collaborative. First, a prospective data collection arm will capture all patients undergoing ileostomy closure in a 3-month period; second, all patients undergoing anterior resection and ileostomy formation over an historical 12 month period will be identified and time to closure or incidence of 'non-closure' calculated. Units will be surveyed to determine local clinical and management protocols and barriers to timely closure.

Outcomes

Outcomes will include average time and national variation in time to ileostomy closure; national and regional incidence of non-closure; and factors impacting time to closure. Results will be presented and discussed with patient and public representatives and national associations to facilitate development of consensus guidelines on optimum treatment pathways to reduce time to closure. Guidelines will be presented to relevant stakeholders with a view to national implementation, policy and practice change.

Measuring success

Success of the project will be high quality data collection of >90% of patients included in the study, with the ultimate measure demonstrated by a reduction in time to closure of ileostomy. This would be measured by a follow-up snapshot interval re-audit. Surrogate measures of success will be achievement of our stated aims: to identify time to closure and incidence of

non-closure; to identify factors impacting time to closure and develop and implement guidelines to reduce delays to closure. Local and national uptake of guidelines thus demonstrating a change in policy and practice will provide the best indicator of project success.

Background Literature

Rectal cancer is common, with over 11,000 cases each year in the UK [1]. The gold standard surgical treatment for mid to low rectal cancers is sphincter sparing anterior resection. During this, a temporary ileostomy is commonly formed to cover the pelvic anastomosis. Such practice aims to reduce the incidence and sequelae of anastomotic leak, which include increased morbidity, mortality and prolonged hospital stay [2]. Unless precluded by patient comorbidity or patient preference, patients will undergo interval closure or reversal of ileostomy, thus restoring bowel continuity. Standard timing for reversal is considered to be 3 months, yet there is limited evidence to inform optimal time of reversal, with recent evidence suggesting that reversal may be safely performed as early as the first month following initial surgery [3]. In practice, reversal of ileostomy is a benign procedure without a cancer driven target in the UK and as such may be delayed due to a variety of factors including patient recovery, post-operative complications or chemoradiotherapy, as well as service demand pressures.

As oncological outcomes from cancer surgery have improved, survivor patient reported outcome measures, including quality of life, have gained increasing relevance. A report commissioned by Department of Health as part of the National Surviving Cancer Initiative demonstrated that 19% of bowel cancer patients had difficulty controlling their bowels, confirming previous published reports [4, 5]. Unsurprisingly, these symptoms have a profound impact on patients' quality of life, with those patients suffering bowel dysfunction twice as likely to report lower quality of life [6]. Reported symptoms of bowel dysfunction following bowel resection range from stool fragmentation and emptying difficulties, to faecal urgency and incontinence. In the context of rectal cancer surgery these symptoms are often referred to as Low Anterior Resection Syndrome (LARS) [7], with over half of such patients reporting major LARS symptoms [8].

Crucially, a recent study reported that delay to closure of ileostomy of greater than 6 months was associated with a 3.7 fold-increase risk of major bowel dysfunction after restoration of bowel continuity [8]. These data support a previous report which demonstrated a two-fold increased risk of bowel dysfunction as measured by the Wexner score [9] and concurrent

significant decrease in quality of life in those where ileostomy was closed more than 3 months following index surgery [10]. Despite this, time to closure of ileostomy varies widely across Europe, and is not subject to national targets or financial incentives within the NHS. Indeed, in mainland Europe and the USA closure > 3 months after initial surgery is considered late [11], while in the UK 34% of ileostomies following anterior resection are still not closed at 18 months [12].

Of course, delay to closure impacts not only bowel function and quality of life following restoration of continuity, but is also associated with patient distress and risk of serious complications whilst the temporary ileostomy is in situ. A recent large patient consultation exercise undertaken in conjunction with the ACPGBI found that patients 'put their lives on hold' whilst waiting for ileostomy closure [13], whilst dehydration, renal failure, hospital readmission and local skin complications are also common in such patients [14, 15]. The economic cost to delayed closure is clear- complications requiring hospital admission result in significant cost to the health service, yet even routine costs such as stoma appliances and district nursing care incur large cumulative costs across the many thousands of patients waiting for ileostomy closure.

Whilst clinical factors might preclude timely closure, it is possible that surgeon and patient preference, bed shortages or service pressures due to competing national targets e.g. cancer waiting times, might influence time to closure, yet no study to date has evaluated such factors. However, timely closure is achievable within the modern NHS- an approach that sees ileostomy closure as a continuation of the cancer pathway and a policy whereby patients are given an agreed date for closure on discharge from hospital after their index operation results in significant reduction in interval to closure [16]. Whilst this approach was of benefit in the author's practice, a full picture of factors impacting interval to closure is required to develop strategies that can be implemented across the UK. A recent pan-European audit undertaken by the European Society of Coloproctology, captured 2527 operations involving reversal of ileostomy/colostomy yet focused primarily on anastomotic technique and will not yield data on timing/delay to closure (unpublished). Therefore there is an urgent need for a multicentre UK audit to determine average time to ileostomy closure and factors contributing to delays to closure.

We hypothesise that delay to closure of ileostomy is common in UK surgical practice and that hospital processes increasing waiting times for postoperative outpatient review, relevant investigations and elective surgery significantly impact time to closure. Our hypothesis continues that units which report low intervals to ileostomy closure will demonstrate

streamlined patient pathways to closure which can be incorporated into consensus guidelines for full national implementation.

Context for the Research

To date, research in this domain has focussed on the impact of delayed closure of temporary ileostomy [8, 10], yet with no consideration of the causes of such delays. A recent, large multi-national audit of ileostomy closure undertaken by the European Society of Coloproctology focused primarily on anastomotic technique and will not yield data on timing/delay to closure (unpublished). The problem (i.e. delayed closure) and the consequences (bowel dysfunction) are clear yet the root causes of the problem remain unclear and so solutions cannot be devised. This study is focused on identifying the factors underlying delayed ileostomy closure. These data will fill the current knowledge gap, allow consensus solutions to be produced and best practice guidelines to be devised and implemented.

Aims and objectives

The aims of the study are:

- To calculate the average time period between formation and closure of ileostomy, following anterior resection for rectal cancer, in the UK
- To ascertain the causes of delays in closure of ileostomy
- To develop guidelines outlining optimum treatment pathways following ileostomy formation, thereby streamlining care and reducing delays in closure.

In order to achieve these aims our objectives are:

- Prospectively collect data on all patients undergoing closure of ileostomy (following anterior resection for rectal cancer) during a three-month period.
- Investigate causes of delays by surveying centres in order to determine local clinical and management protocols and barriers to timely closure, (including clinical factors, surgeon and patient preferences and service delivery issues). Specifically, units with best-practice will be identified and protocols reviewed.

- Review records from an historical 12-month period of all patients undergoing anterior resection and ileostomy formation, to calculate time to closure or incidence of 'non-closure' in a large national cohort.
- Develop consensus guidelines on optimum treatment pathways following ileostomy formation with a view to national implementation, to improve the bowel function and quality of life of patients treated for rectal cancer.

Outcomes

Primary outcomes

Average duration to closure of ileostomy from index cancer resection surgery

Incidence of non-closure at 18 months

Secondary outcomes

Factors contributing to delay to closure of temporary ileostomy

Incidence of complications after ileostomy closure

Pathways contributing to expedient ileostomy closure

Methods

Researchers

UK surgical trainees will collect data through the trainee collaborative network, led by the Dukes' Club (the trainee arm of the ACPGBI). Recruitment of investigators and collaborators will be led through the Dukes' Club, who will also ensure that all trainees have been educated in the methodology of the study as well as data collection to ensure good homogeneity between investigators; there will be both written material and a study education day prior to the start of the data collection period (March 2018).

Study design

There will be two parts to the study; 1) a prospective 3-month data collection of all patients undergoing closure of ileostomy following a previous anterior resection for rectal cancer and 2) a retrospective data collection of patients who underwent anterior resection with ileostomy formation from 2015-2016.

Patient identification and selection:

Part 1) Patients will be identified prospectively from elective waiting lists by local lead investigators. Inclusion criteria: patients over the age of 18 at the time of their initial anterior resection; patients having an ileostomy formed during an anterior resection for rectal cancer who are due to undergo ileostomy closure in the three-month period of data collection (April – June 2018).

Part 2) Patients will be identified from prospectively maintained electronic theatre records. Inclusion criteria: Patients over the age of 18 who underwent anterior resection and ileostomy formation for rectal /rectosigmoid cancer between January 1st 2015 and December 31st 2015.

Quantitative methods

Data will be collected from electronic hospital and theatre records, MDT notes and radiology imaging systems. Case Reporting Forms (CRFs) will capture information on patient demographics, oncological details, surgical history and outcomes. We have already secured support from the Research Design and Conduct Service (RDCCS) to provide methodological assistance. Data will be returned through the secure REDCap server, as successfully used in several previous national audits and will be pseudoanonymised, with the key held locally at

each participating centre. Data collection in hospital and electronic capture on REDCap will be piloted in January 2018 to test all procedures and processes and any problems identified will be addressed.

Data fields collected on CRF (Appendix 1)

- Patient age
- Patient gender
- Hospital
- Consultant
- Use of neo +/- adjuvant chemotherapy +/- radiotherapy
- Method of primary surgery (laparoscopic vs. open)
- Tumour level from anal verge (on MRI – pre neoadjuvant therapy if applicable)
- Imaging performed prior to ileostomy closure (e.g. water soluble contrast enema)
- Clinic appointment prior to closure
- Date of entry onto waiting list
- Presence of anastomotic leak following anterior resection requiring either radiological/endoscopic intervention or re-operation
- Number of days from primary surgery to a) waiting list entry and b) closure
- Patient outcomes (90-day complications -Clavien-Dindo classification, 30-day readmission, return to theatre)
- Other relevant factors impacting time to surgery (e.g. documented patient preference,

Data Management

Access to data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Data Recording and Record Keeping

Clinical data will be entered into the electronic database by delegated investigators or research nurse working at each hospital site. Staff in the trial office will work closely with the site staff to ensure that the data are as complete and accurate as possible. An extensive range of consistency checks will further enhance the quality of the data.

Participant Confidentiality

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's personal details (name, address) will be stored by sites under the guidelines of the 1988 Data Protection Act and not entered onto the trial database. Participants will be allocated an individual specific trial number and this, along with age, gender and local study ID will be used to identify their data on the CLOSE-IT trial database. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

Reporting

The Chief Investigator (CI) shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Archiving

The Trial Master File (TMF) containing essential documents will be archived at an approved storage facility for a minimum of 5 years after end of trial. The Principal Investigators at each site are responsible for archiving the Investigator Site File (ISF) and essential documents pertaining to the trial for the same duration. Trial data must not be destroyed without written permission from the Sponsor, who is responsible to ensuring trial data is archived appropriately.

Quality Assurance Procedures

The study will be monitored in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Ethical considerations and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of Good Clinical Practice and in accordance with all applicable regulatory guidance.

This protocol and related documents (and any subsequent amendments) will be submitted for review to Research Ethics Committee Wales. Annual progress and safety reports and a final report at the conclusion to the trial will be submitted to the REC within the timelines requested.

The study will respect the rights of participating patients and ensure confidentiality of patient information. Patients undergoing surgery for colorectal cancer have an excellent support system through the specialist cancer nurses and the clinical team, as well as several charities and voluntary organisations. Should participants have additional questions about the trial, advice will be available from both within the research team and outside of the research team in the form of websites such as the nhs website page: Clinical trials and medical research - Joining a trial, found on <http://www.nhs.uk/Conditions/Clinical-trials/Pages/Takingpart.aspx>.

Definition of End of Study

The end of the study will be at 90days after the 3 month data collection.

Data analysis

Time to ileostomy closure and the incidence of prolonged delay to closure will be analysed by basic descriptive statistics. Putative factors associated with time will be investigated. Causes of delay will be stratified as clinical or service, to enable differentiation of units with good practice who incur delays due to clinical factors, from those units where service barriers, such as lack of theatre availability, have caused delays.

As there are not comparative outcomes or patient groups within this study, a formal power calculation has not been performed. We have based our patient group sizes upon engagement of surgical trainees as investigators in prior national audit studies; Investigators will be sought from across the UK, with our aim to establish data collection from at least 40 centres, with each centre aiming to collect data from 5 prospective patients and 15 retrospective patients. Identification of patients and collection of data will be closely monitored leading up to and during the active data collection period.

Part 1) 3-5 patients/centre with approx. 40centres = 200 patients

Part 2) 15 patients / centre with approx. 40 centres = 600 patients

Inclusion criteria

Part 1)

Patient aged 18 or over

Patient with previous anterior resection for rectal cancer with defunctioning ileostomy

Patient undergoing elective reversal of ileostomy during three-month prospective study period

Part 2)

Patient aged 18 or over

Patient with previous anterior resection for rectal cancer with defunctioning ileostomy performed between January 1st 2015 and December 31st 2015.

Exclusion criteria

Patient not meeting above inclusion criteria

Identification of patients

Part 1) Patients will be prospectively identified by local study leads by interrogation of theatre operative lists over the three-month data collection period.

Part 2) Patients who have had an anterior resection and defunctioning ileostomy for rectal neoplasia from January 1st 2015-December 31st 2015 will be identified by study leads from local departmental databases, theatre lists and outpatient clinics.

Timetable for project

Month 0-3	Ethical application - approval
Month 0-3	Limited pilot feasibility study to trial patient identification and data collection processes (Part 1- n=3 centres; Part 2- n=3 centres)
Month 0-3	Study promotion via ACPGBI, Dukes' and NRC, social media and web-based newsletter
Months 0-3	Development of website to provide
Months 3-9	3-month local data collection capture and submission for Part 1, with 3-month follow-up period to capture 90-day complications
Months 3-9	Local data collection capture and submission of retrospective (part 2) cases
Months 10-12	Analysis of quantitative data
Month 13-15	Report writing & Considering next steps

Feasibility of project

Preparation for the project is already underway with a view to commencing the 3-month period of data collection in April 2018. We therefore have sufficient time to pilot procedures and processes for the study and to identify and rectify any issues.

Infrastructure: Trainee led national research collaboratives have gained increasing momentum in recent years. Following the success of numerous national studies, there is now a well-established network of trainees who are experienced in contributing to such research. The Dukes' Club is already engaging its members in research and promoting active participation in trial recruitment. Other forms of infrastructure necessary for the successful completion of the study are also already in place e.g. REDCap, the database that data will be entered into at each participating centre, is already available at the lead site while administrative and logistical support has already been secured through engagement with R and D at the lead site.

Support: We have engaged with the Research & Development department at the lead site from an early stage of study conception and are following their advice regarding the study set-up and design. They have agreed to provide all necessary practical, administrative and logistical support as required. In addition to their support we will apply for portfolio adoption in Wales, thereby increasing resources available to us such as research nurse time etc. Similarly, we will seek help from clinical research network (England) to support the study throughout the UK.

Feasibility & Acceptability: We do not feel that there are any significant ethical considerations with this study. Following advice from the local R and D department an application for proportionate ethical review is now in progress. With regards to data collection feasibility, we have widely consulted with colorectal surgeons and trainees, who will themselves be collecting data, and with patients with an ileostomy (please see PPI section) and from this consultation believe the study design to be both wholly acceptable and our aims fully achievable.

Public/Patient Involvement Plans

We acknowledge that patient and public involvement in setting research priorities and in informing study design ensures research is fully focused on issues important to patients. Patients have loudly called for more research into temporary ileostomy and anterior resection syndrome- attendees at the ACPGBI PPI consultation commented that having a temporary

stoma meant 'putting life on hold' [13], with suggestions that delay to closure delays the return to normal activities and psychological recovery. Meanwhile, patient discussion forums provide a clear indication of the distress caused by symptoms following ileostomy closure- 'I have had dreadful anterior resection syndrome symptoms ever since my stoma reversal a year ago... every day is a challenge...I can't get a job because of ... unpredictability of visits to the loo' (www.Macmillan.org.uk), and the frustration of long delays to closure - 'I am still bloody waiting for my reversal! Next week will be 5 months since I was told I was on the waiting listit's over a year since my op now..... I cannot book holidays...'

The study design and proposal has already obtained PPI: The original study concept and design has been informed by qualitative interviews of patients with LARS undertaken by one of the Co-investigators [8]; 'Involving People' network have approved the project and will provide continued input; the design and lay summary have been peer reviewed by the University of Edinburgh Patient and Public Involvement Advisor and lay volunteer. Finally, the study question and design has been reviewed by a patient of SP who believes that it is important *'this debilitating condition (LARS), and the reasons why it occurs are investigated'...**'people believe that when they are told they are clear of Cancer that everything will be okay and back to normal. That is far from the truth as we know.'* This patient will continue to advise on study design and dissemination.

PPI will be most fully involved in the development of best practice guidelines- we will include patients on steering committees and in consensus seeking groups. During this phase, we will ask patients how and when they believe reversal should be discussed and undertaken. We know that prior work has demonstrated timely closure when operation dates are given at index discharge [16], yet given the distress and upheaval following the index surgery this may not be appropriate. We will ask patients if they want to see the surgeon in clinic first (which may delay reversal), or whether timely reversal is more important.

The Dukes' club has close links with various local and national patient liaison groups, including 'Involving people' and the ACPGBI PLG – both of whom have already agreed to provide meaningful PPI at every stage of the study from final design to analysis and future direction. To achieve our final aims we will ask patients to promote findings from the research, to raise awareness of the impact of delayed closure and guidelines for best practice. Full patient engagement and promotion will be critical to ensuring derived best practice guidelines are widely accepted and implemented.

How will the results of this study be used?

Through this study, we will identify units across the UK who provide an efficient and timely pathway for patients requiring reversal of defunctioning ileostomy following anterior resection. The results from this study will be widely disseminated to the scientific and clinical community as well as patient groups through ties to the ACPGBI and other patient focused groups and charities. We would expect results from the study to be presented at national and international level and to be published in a high impact scientific journal with open access. Crucially, we intend that results will be used to inform consensus guidelines on optimum treatment pathways following ileostomy formation. Guidelines will be widely presented with a view to national implementation and the ultimate aim of improving the bowel function and overall quality of life of patients treated for rectal cancer. For some, these guidelines will affirm current practice, while for other units, the guidelines will provide a framework to overcome barriers to a timely ileostomy closure.

How will the study potentially benefit people affected by cancer

Ultimately, we aim to improve bowel function and thus overall quality of life following closure of ileostomy, in patients who have undergone surgery for rectal cancer.

During the operation to resect a rectal cancer, a defunctioning ileostomy is often formed to divert faeces away from the anastomosis while it heals. Delay in carrying out a second operation to close the ileostomy can have a deleterious effect on bowel function which can leave many patients with impaired quality of life despite being cured of cancer. Focusing not only on the treatment of cancer, but also on the after-effects of cancer survivorship is critical in improving outcomes for these patients.

Through ascertaining the severity of the problem, i.e. how long the delays are, and by investigating barriers to timely closure, (including clinical and management protocols, service provision issues etc.), we will develop consensus guidelines on optimum treatment pathways following ileostomy formation. These guidelines will streamline patient care and minimise delay to ileostomy closure, and will thereby improve bowel function and overall quality of life of patients treated for rectal cancer.

The guidelines will be presented and published with a view to national implementation-benefitting hundreds of patients treated for rectal cancer each year, making a significant and tangible difference to patient care.

Sustainability of the project

Our ultimate aim is to improve the bowel function and quality of life of patients with rectal cancer. To achieve this, our next step following data collection is to create a national consensus on the optimum treatment pathways following ileostomy formation. Our study has been tailored to allow us to complete our aims, including national dissemination of our results.

Further development of this body of work in the future, will include significant focus on patient reported outcomes following ileostomy reversal (e.g. bowel function) and the individual factors, including delay to closure, which may adversely affect this.

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Appendix 1 CRF

Study centre	
Patient study ID	
DOB	
Gender	
Consultant	
Level from anal verge (first MRI scan)	
Neo-adjuvant	No Yes -short-course RXT chemorad.
Adjuvant	No Yes
Index surgery	Date
Index surgery mode	Open Lap No ERAS ERAS
Anastomotic leak after index surgery	No Yes - conservative Rx, percutaneous drainage, re-operative
Imaging performed prior to ileostomy closure	No Yes - CT AXR with contrast Other
Clinic appointment prior to closure	No Yes- date of clinic date of entry onto clinic waiting list
Date of entry onto waiting list	
Number of days from primary surgery to a) waiting list entry and b) closure	
Date of closure	
Closure complications	No Yes – date, what, CD score
Latest follow-up	Date Complications
Documented factors delaying closure	Patient preference, patient unavailability, surgeon unavailability
Other factors delaying closure	Patient morbidity,