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## The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP): study protocol

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## The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP): study protocol

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## Abstract

### Introduction

Although colorectal cancer outcomes in England are improving they remain poorer than many comparable countries. Yorkshire Cancer Research have, therefore, established a Bowel Cancer Improvement Programme (YCR BCIP) to improve colorectal cancer outcomes within the Yorkshire and Humber, a region representative of the nation in these terms. It aims to do this by quantifying variation in practice, engaging with the colorectal multidisciplinary teams (MDTs) to understand this and instigating interventions to minimise it and improve outcomes.

### Methods and analysis

Initially, routine health datasets will be used to quantify variation in the demographics, management and outcomes of patients across the Yorkshire and the Humber region and results presented to MDTs. The YCR BCIP is seeking to supplement these existing data with patient reported health-related quality of life information (PROMs) and tissue sample analysis. Specialty groups (surgery, radiology, pathology, clinical oncology, medical oncology, clinical nurse specialists and anaesthetics) have been established to provide oversight and direction for their clinical area within the programme, to review data and analysis and to develop appropriate educational initiatives.

### Ethics and dissemination

The YCR BCIP is seeking to address the variation in practice to significantly improve colorectal cancer outcomes across the Yorkshire and Humber region. PROMs and tissue sample collection and analysis will help to capture the information required to fully assess care in the region. Engagement of the region's MDTs with their data will lead to a range of educational initiatives, studies and clinical audits that aim to optimise practice across the region.

## Strengths and limitations of this study

- Evaluating variation in the management and outcomes of colorectal cancer patients using routinely collected clinical datasets and new information on aspects of care not currently quantifiable through existing datasets.
- Providing regional colorectal MDTs with data and, with their input, develop interventions to minimise any variation seen in order to optimise outcomes.
- Facilitating implementation of guidelines such as routine screening for Lynch syndrome and deficient mismatch repair status.

## Introduction

Colorectal cancer is a common disease in the UK with over 41,000 people diagnosed each year and 16,000 people dying from it. Although survival rates have improved over time, they continue to lag behind those attained by many economic neighbours[1] and so developing interventions to improve outcomes is a priority.

Some potential explanations for these survival differences include variability in the quality of care and access to services. For example, local recurrence and survival rates in rectal cancer are related to the quality of the surgical resection[2] so improving surgical quality is likely to improve outcomes. Likewise, ensuring gold standard diagnostic, staging and multidisciplinary care across all aspects of the patient pathway have a demonstrable impact on outcomes[3] while screening for Lynch syndrome and deficient mismatch repair will enable more effective management of patients.

Other countries have acknowledged these relationships and taken steps to improve standards. For instance, in the early 1990s, Norway recognised there was huge variation in local recurrence rates depending on which surgeon operated. In response, they initiated a training programme to quantify variation and improve the quality of surgery. This strategy was a success, reducing local recurrence and improving overall survival[4]. As a result similar programmes in other countries, including the UK [3, 5-9] were established with equally positive outcomes including lower postoperative mortality and better survival, lower permanent stoma and local recurrence rates, better preoperative staging, improved selection of patients for non-surgical treatment and the need for less emergency surgery.

Whilst these programmes have undoubtedly had a positive impact, variations in management remain and particularly so in the UK. Here, although outcomes have improved, the gap to rates attained in comparable countries[10] have not closed. Better understanding of what is driving these variations will help to target interventions to improve care.

Yorkshire Cancer Research is a charity whose aim is to ensure that more people of Yorkshire avoid, survive and cope with cancer and, by 2025, they intend to have reduced cancer deaths in the region by 2,000 per year. As part of their strategy to achieve this they have recently funded the Bowel Cancer Improvement Programme (YCR BCIP). This initiative

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3 builds upon the experience gained from several English National programmes [8, 9] and  
4 extends the approach of those successful programmes completed in Scandinavia [3, 5, 6]. It  
5 centres on the collection and analysis of robust colorectal cancer data to quantify practice  
6 across the region, ensuring the multidisciplinary teams (MDTs) managing the disease engage  
7 with these data and agree areas for improvement. Educational interventions or other  
8 strategies can then be implemented to ensure optimal practice is achieved.  
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14 The aims of the YCRBCIP study are to:

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17 1. Quantify and report the variation in the demographics, management and outcomes  
18 of the region's colorectal cancer patients using  
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20 a. routinely collected clinical datasets,  
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22 b. new information on aspects of care not currently quantifiable through  
23 existing datasets (e.g. Patient Reported Outcome Measures (PROMs), the  
24 molecular subtyping of the disease and the quality of radiology, pathology  
25 and surgery).  
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29 2. Where comparative data are available, to determine how outcomes from the  
30 Yorkshire and Humber region compare to the rest of England.  
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- 33 3. To provide the Yorkshire and Humber region colorectal MDTs with these data and,  
34 with their input, develop interventions to minimise any variation seen in order to  
35 optimise outcomes  
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- 38 4. Facilitate routine screening for Lynch syndrome and deficient mismatch repair  
39 status.  
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- 42 5. Evaluate improvement in outcomes over the study period.  
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## Methods and analysis

### Setting

The Yorkshire and Humber region of the UK has a population of approximately 5.7 million with around 3,300 colorectal cancer diagnoses a year, amounting to just over 10% of English diagnoses. Patients diagnosed with colorectal cancer in the region are managed by 16 different MDTs. These operate across 14 National Health Service (NHS) Trusts which provide health services for particular geographical areas of the region which exhibit a range of workloads, ranging between approximately 120-390 cases a year (4%-12% of the regional workload). Patients within the geographical areas covered by each Trust exhibit a variable range of demographic features such as socioeconomic deprivation and comorbidity [11].

### Programme design overview

YCR BCIP will interrogate routinely collected NHS data and, subject to patient consent, additional data collected specifically for the programme. Baseline performance outcomes for each MDT from across the region will be assessed. The knowledge will be fed back to each MDT and a programme of educational interventions developed based on the performance outcomes. The process will be iterative as outlined in Figure 1. The programme will run from 1<sup>st</sup> April 2016 until 31 March 2021.

### Clinical specialities

Following a regional meeting of MDT representatives to discuss, plan and agree to programme participation held in June 2016, six specialty groups were initially established. The remit of these groups is to provide oversight and direction for their clinical specialty within the programme, to review data and analyses and to develop appropriate educational initiatives. The six groups focused on the main clinical disciplines involved in the MDT; surgery, radiology, pathology, clinical oncology, medical oncology, and specialist nursing. Group membership was drawn from all of the region's MDTs and an individual established from each to act as a coordinator between the research team and MDT. The need for a separate anaesthetics workstream was subsequently identified and introduced.

### Data collection

Although broad ranging, it was recognised that the routine colorectal cancer data available is not sufficient to quantify all aspects of care robustly. Whilst routine data provides good



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3 information available on 'hard' outcomes such as which operation was undertaken or  
4 survival time, there is a lack of information on what this really means to the individual  
5 concerned and the quality of that survival. This precludes the production of the rich  
6 intelligence the MDTs want to fully understand variation in care. Therefore data collected in  
7 YCR BCIP will come from two main sources:  
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- 10 1. routinely collected NHS datasets,
- 11 2. additional data collected subject to patient written informed consent;
  - 12 a. PROMs data, collected directly from patients on health-related quality of life at  
13 both the time of diagnosis (and before primary treatment if possible) and again  
14 at 12 months post diagnosis.
  - 15 b. Molecular testing of excess pre-treatment diagnostic biopsy tissue, excess  
16 tissue following surgical resection, (both tumour and tumour-associated  
17 normal mucosal tissue), and excess tissue following the biopsy or resection of  
18 distant metastases.
  - 19 c. Screening for Lynch syndrome and deficient mismatch repair on routinely  
20 diagnosed bowel cancers.

### 21 22 23 24 25 26 27 28 29 30 31 32 33 **Routine NHS data**

34 The YCR BCIP seeks to make maximum use of routine NHS datasets and these are brought  
35 together in the UK Bowel Cancer Intelligence Hub[12] where data from the National Cancer  
36 Registry and Analysis Service (NCRAS)[13] are linked to other datasets relevant to colorectal  
37 cancer to provide the richest data possible and enable analysis of the full cancer pathway.  
38 These include, but are not limited to: Hospital Episode Statistics, Radiotherapy Dataset,  
39 Systematic Anti-Cancer Therapy Dataset and Routes to Diagnosis. This will provide both  
40 regional data (around 3,300 cases per year) and comparative national data (around 28,700  
41 cases per year) on patient and tumour characteristics, treatment choices, diagnosis  
42 pathways and patient outcomes. This data will cover ten years preceding the start of the  
43 programme to provide a baseline and be routinely updated to assess changes throughout it.  
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### 53 **Data collected requiring patient written informed consent**

#### 54 ***Participants***

55 All MDTs in the region have been invited to participate in this element of the YCR BCIP.

56 Every colorectal cancer patient (ICD10 C18-C20) is eligible if they are considered suitable for  
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3 treatment, English language literate, aged at least 18 years old and with capacity to give  
4 informed consent. Participants will be asked to consent to the study prior to  
5 commencement of primary treatment or following an emergency intervention.  
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### 8 9 **Sample size**

10 Based on the number of diagnoses per year, there is potential to consent approximately  
11 8,250 patients from sites across the region over a 30 month recruitment period. However  
12 due to eligibility restrictions, consent by MDT and by individuals, administrative/practical  
13 issues and staggered site recruitment start dates, the participation rate is likely to be less.  
14 Using estimates based on previous studies [14, 15] the consent rate is estimated to be  
15 around 42% and the an attrition rate of approximately 35% at the 12 months follow-up  
16 point, giving a sample size of at least 1200. This will provide MDTs with a comprehensive  
17 descriptive profile of their patients in terms of quality of life outcomes; more complex  
18 analyses will be undertaken if sufficient numbers are accrued.  
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### 27 28 **Patient recruitment**

29 This research project is adopted by the NIHR Yorkshire and Humber Clinical Research  
30 Network and therefore recruitment will be undertaken across the region by network  
31 research and clinical staff working collaboratively. Recruitment will run over a 30 month  
32 period.  
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37 Eligible patients will be identified and approached in two ways.

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39 1. Identified via the MDT and informed about the study by consultant letter sent  
40 out with their appointment letter for the primary pre-assessment clinic visit . Where  
41 possible, patients will be approached about the study at this clinic appointment. Patients  
42 missed at this appointment will be contacted at the earliest convenient time point and  
43 informed about the study.  
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49 2. Identified by their NHS clinical team if they present as an acute admission (for example  
50 with a bowel obstruction) and informed about the study by their clinical team following the  
51 emergency intervention (e.g. surgery).  
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54 Interested patients will be provided with full study information (written and verbal). Written  
55 consent may be taken at the time of this approach but patients will be given up to a week  
56 to think about study participation. Patients who wish to join the study will be asked to read,  
57 complete and sign a consent form, including their contact details name, address and/or  
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3 email address. The person taking consent will also record the patient's date of birth, NHS  
4 number and gender.  
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### 6 7 ***Patient participation***

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9 Participants will have the option of completing the PROMs either online (ePROMs) using the  
10 University of Leeds secure questionnaire administration system QTool [16], accessed via the  
11 study website, ([www.YCRBCIP.leeds.ac.uk](http://www.YCRBCIP.leeds.ac.uk)) or on paper (pPROMs) with a pre-paid return  
12 envelope. They will be asked to complete the survey as soon as possible after consenting,  
13 this may be completed while attending hospital at the time of consent or later at home. Just  
14 prior to the 12 month follow-up the patient status will be checked via NCRAS to confirm that  
15 the patient is still alive. Patients will then be sent an email/letter 12 months post-diagnosis  
16 by the YCR BCIP research team, inviting them to complete PROMs again (on paper or online  
17 according to patient preference). At both time points reminder letters or emails will be sent  
18 at two weeks and followed up two weeks later (if no response) with the survey being resent  
19 with the reminder letter. The process is outlined in Figure 2. Tissue samples removed at  
20 surgery or biopsy which are surplus to routine clinical requirements will be utilised by the  
21 research team for upfront testing of novel biomarkers.  
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### 33 34 ***Management of consent and follow-up procedures***

35 Participant recruitment will be undertaken by each Trust involved in the study. Each  
36 research network site will allocate a study ID for potential participants. They will use a  
37 University of Leeds secure electronic transfer system every two weeks to inform the YCR  
38 BCIP research team of all recruitment activity. This will include the consented patients  
39 contact details, date of birth and NHS number to allow for follow-up and to ensure tissue  
40 blocks are appropriately labelled for tracking and data linkage. All subsequent participant  
41 contact will be undertaken by the central YCR BCIP team.  
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### 48 49 ***Patient Reported Outcome Measures (PROMs)***

50 Participants will be asked to complete a range of validated generic, cancer-specific and  
51 colorectal cancer-specific PROMs in addition to socio-demographic characteristics. Content  
52 has been informed by: clinical relevance, opinion of service users, overall length and  
53 participant burden[17], reviews of questionnaires measuring quality of life in colorectal  
54 cancer patients[18-22] and UK recommendations for the core outcomes set for trials in  
55 colorectal cancer surgery[23].  
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The survey comprises four sections at baseline and five sections at follow-up. The same PROMs are included at both time points. In addition, at the second time point (12-months post diagnosis) participants will be asked to complete questions about the financial costs of cancer. The time taken to complete the survey is estimated is about 30-35 minutes.

*Section One: Your overall health and quality of life (both time points)*

- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30, the colorectal cancer specific module and items from the prostate, endometrial and cervical cancer modules [24-28]
- EuroQol Group EQ-5D-5L [29]

*Section Two: Your everyday life and well-being (both time points)*

- Social Difficulties Inventory (SDI-21) [30, 31]
- The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [32, 33]

*Section Three: Managing your health (both time points)*

- Self-efficacy for Managing Chronic Disease [34]
- The Brief Illness Perceptions Questionnaire (B-IPQ) [35]

*Section Four: The financial cost of cancer (Time 2 only)*

- A questionnaire developed in-house based on one used in the ePOCS study[36].

*Section Four: Questions about you (Time 1) and Section Five: Questions about you (Time 2)*

- Self-report socio-demographic and clinical details

***Tumour and normal mucosal tissue samples***

The tissue samples to be collected for this study are:

1. excess pre-treatment, diagnostic biopsy tumour tissue
2. excess tissue following surgical resection (tumour and tumour-associated normal mucosal tissue)
3. excess tumour tissue following the biopsy or resection of distant metastases

The tissue samples will be formalin-fixed and paraffin wax-embedded as per the routine histopathology procedures at the patients' hospital. Tissue blocks will be used for any routine clinical diagnostic procedures required by the hospital before being sent to Pathology at the University of Leeds, and will be available to return to the hospital for further clinical testing if required.

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3 YCR BCIP will test for novel or rare potentially treatable targets via a range of molecular  
4 techniques. The immunohistochemical markers of interest include, HER2, PTEN, PD-1 and  
5 PD-L1, amphiregulin and epiregulin, and immune system markers CD3 and CD8. The study  
6 will also undertake phenotype analysis by using high-resolution scanned images of tumours  
7 using novel algorithms to identify improved prognostic and predictive markers of outcome.  
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12 Next Generation Sequencing and/or pyrosequencing will be performed on any extracted  
13 DNA to identify tumours with specific gene hotspot mutations including, KRAS, NRAS, BRAF,  
14 EGFR and PIK3CA. Other molecular markers linked to causation, outcome and response to  
15 therapy will also be investigated e.g. bacterial toxin carriage or fusobacterium nucleatum.  
16 Analysis of RNA expression levels of receptor ligands such as amphiregulin and epiregulin,  
17 and HER2 and HER3 may also be performed.  
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22 Patients are asked to consent to their clinical team being informed in the event that  
23 clinically relevant laboratory results are found. This includes the possibility of hereditary  
24 conditions identified through tumour testing e.g. Lynch syndrome or deficient mismatch  
25 repair status. These will be confirmed through routine NHS Clinical Genetics testing after  
26 counselling following referral from the local clinical teams with no germline testing taking  
27 place through the programme.  
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### 35 36 **Data analysis**

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38 Baseline assessments of care in the region are to be performed on individuals diagnosed  
39 with colorectal cancer (ICD10 C18-C20) in Yorkshire and the Humber, enabling comparison  
40 between teams in the region and with national data[11]. Initially this includes using  
41 descriptive analysis and statistical methods such as survival analysis and funnel plots [37]  
42 comparing the following data:  
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47 • demographic characteristics (age, gender, socioeconomic status (income domain of  
48 the Index of Multiple Deprivation [IMD] 2010) and Charlson comorbidity level);
- 49  
50 • tumour characteristics (site and stage of disease);
- 51  
52 • surgical management (major resection, 18-month permanent stoma following major  
53 resection, laparoscopic surgery for major resections and abdominoperineal excision  
54 rates);
- 55  
56 • outcomes (30-day postoperative mortality and 3-year survival, PROMs);  
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- use of neoadjuvant radiotherapy and timing of the proceeding surgery;
- use of adjuvant chemotherapy.

Some analyses will be rerun periodically over the course of the programme to evaluate the impact on outcomes of specific educational interventions.

The routinely collected NHS datasets and the newly collected PROMs and tissue data will be brought together through the UK Bowel Cancer Intelligence Hub. Descriptive statistics will be used to report the survey results and assess the quality of life outcomes of the participants. The outcomes will be analysed according to stage of disease, treatment type, comorbidity, age, ethnic and sociodemographic group (and other relevant variables). These descriptive analyses will identify potential relationships of interest which can be investigated further. Regression modelling will be used to investigate associations amongst the different types of variables to identify statistically and clinically significant risk factors and predictors of outcomes. In order to be robust, analyses will require appropriate adjustment for case-mix and other confounding factors and may require more complex techniques, such as the modelling of hierarchies within the data (multilevel modelling), post-hoc weighting to overcome response bias and multiple imputation of missing data.

### **Intervention**

The analyses will be disseminated and discussed by regional MDTs at events for each clinical discipline. Agreements of educational needs to improve care will be agreed along with any additional data capture and audit processes that teams agree are required. The process is repeated with ongoing data analyses to establish the improvements in management and outcomes that have occurred (Figure 1). As YCR BCIP progresses, further work will be undertaken looking at other outcomes including, but not limited to, those related to screening, pathology and long-term outcomes.

### **Public Patient Involvement**

Patients and carers were actively engaged through the PROMS Working Group to develop the design and content of the patient questionnaires, the patient information sheet and consent form. At the request of the patients and carers, additional questions were included around the financial impact of cancer and a specific request was made to EORTC to amend the EORTC colorectal module and add specific questions from other EORTC modules to

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3 understand side effects of cancer and cancer treatments. EORTC granted these specific  
4 amendments for this study. The electronic and paper copies of the final draft  
5 questionnaires were tested with patients attending a colorectal cancer follow-up clinic at  
6 one of the region hospitals. Modification to the layout of the questionnaires were made  
7 following the results of the testing. The testing gave an understanding of the length of time  
8 it took patients to complete the questionnaires. The PROMS Working Group will remain  
9 active throughout the length of the study; the group will be kept apprised of recruitment  
10 levels and early results. It is expected that the patients will advise on the analysis and how  
11 the results are communicated to the regional clinical teams and wider audiences.  
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## Discussion

The YCR BCIP study ambitiously aims to improve outcomes for patients with colorectal cancer across the Yorkshire and Humber and region by in-depth analysis of existing and newly captured data, and by actively engaging local MDTs. In its initial stages, this will be done by demonstrating the variation in the demographics, management and outcomes in the region using routine NHS datasets. However, given the limitations of what can be achieved with existing data, the YCR BCIP is collecting additional data to analyse alongside this with the purpose to better understand what is driving the observed variation.

The PROMs data will enrich other study data and allow for an 'in-depth' description of what life is really like for colorectal cancer patients at diagnosis and a year later. At present, the patient voice is not 'measured' routinely as part of clinical practice, neglecting the impact of illness and treatment on the everyday lives of patients. YCR BCIP will change this with the integration of PROMs administration into clinical practice[15]. The PROMs used in this study have been selected with input from experts in colorectal cancer and psychosocial care: patients, clinical nurse specialists and doctors. Although the length of the survey would not be feasible to administer in everyday practice, information on which PROMs provide the most meaningful data will be obtained. In the future risk-stratified follow-up may incorporate not only clinical indicators but also key quality of life indicators to inform best supportive care[38].

Results from the tissue collection and testing could impact on treatment and follow-up decisions for the participating patients and, potentially, their families. For example, the results may indicate that a patient could benefit from a targeted treatment being tested through an open clinical trial if they develop an indication for further treatment e.g. Medical Research Council FOCUS4 [39]. Increased risks of having a hereditary condition may be identified, which not only has implications for the patient but also their family.



## Ethics and dissemination

The study was granted ethical approval (17/WM/0374) by the West Midlands – Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research’s portfolio of studies in December 2017 (Project ID 227673).

The YCR BCIP is offering a novel approach to address the variation in colorectal cancer care across a large region of the UK. Engagement of the region’s MDTs with their data will lead to a range of educational initiatives, studies and clinical audits that aim to optimise practice across the region. It is planned that the outcomes of these will be presented to the relevant specialty group for review and to develop actions based on findings. Further work from the seven specialty groups involved in the programme: surgery, radiology, pathology, clinical oncology, medical oncology, nursing and anaesthetics, will be reported soon.

## Authors’ contributions

PQ is the principal investigator. NW, PW and EM are coinvestigators and/or workstream leads. Together these authors conceived and designed the study. HR and JM manage the study. JT provides statistical support. AG provides pathology support. All authors contributed to writing of the manuscript and have approved a final version.

## Competing interests

The authors declare that they have no competing interests.

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4 Institute for Health Research Clinical Research Network (NIHR CRN).  
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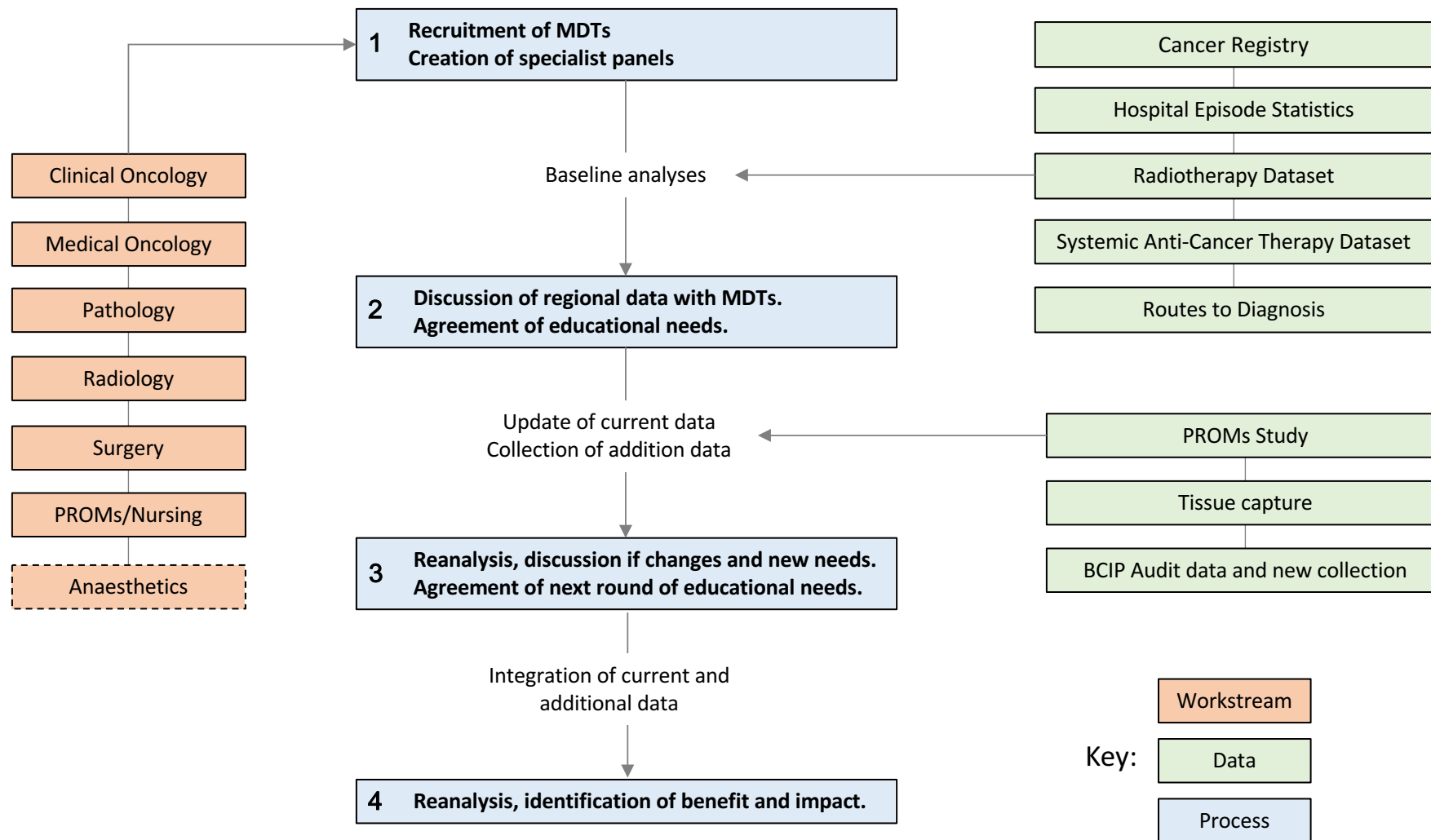
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BMJ Open  
Patient Consented

Baseline Online Questionnaire

Baseline Paper Questionnaire

Completed within 2 weeks?

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

Baseline Questionnaire not Completed?

Baseline Questionnaire Completed?

No follow up at 12 months

12 month death check undertaken

Invitation for online or paper questionnaire at 12 months post baseline

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

12 month Questionnaire not Completed?

12 month Questionnaire Completed?

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# BMJ Open

## The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP): study protocol

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## The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP): study protocol

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## Abstract

### Introduction

Although colorectal cancer outcomes in England are improving they remain poorer than many comparable countries. Yorkshire Cancer Research have, therefore, established a Bowel Cancer Improvement Programme (YCR BCIP) to improve colorectal cancer outcomes within Yorkshire and Humber, a region representative of the nation in these terms. It aims to do this by quantifying variation in practice, engaging with the colorectal multidisciplinary teams (MDTs) to understand this and instigating educational interventions to minimise it and improve outcomes.

### Methods and analysis

Initially, routine health datasets will be used to quantify variation in the demographics, management and outcomes of patients across the Yorkshire and Humber region and results presented to MDTs. The YCR BCIP is seeking to supplement these existing data with patient reported health-related quality of life information (PROMs) and tissue sample analysis. Specialty groups (surgery, radiology, pathology, clinical oncology, medical oncology, clinical nurse specialists and anaesthetics) have been established to provide oversight and direction for their clinical area within the programme, to review data and analysis and to develop appropriate educational initiatives.

### Ethics and dissemination

The YCR BCIP is seeking to address the variation in practice to significantly improve colorectal cancer outcomes across the Yorkshire and Humber region. PROMs and tissue sample collection and analysis will help to capture the information required to fully assess care in the region. Engagement of the region's MDTs with their data will lead to a range of educational initiatives, studies and clinical audits that aim to optimise practice across the region.

## Strengths and limitations of this study

- A novel approach by providing regional colorectal MDTs with data and, with their input, develop educational interventions to minimise any variation seen in order to optimise outcomes.
- Evaluating variation in the management and outcomes of colorectal cancer patients by combining routinely collected clinical datasets and novel information on aspects of care not currently quantifiable through existing datasets.
- The study will facilitate implementation of guidelines such as routine screening for Lynch syndrome and deficient mismatch repair status.

## Introduction

Colorectal cancer is a common disease in the UK with over 41,000 people diagnosed each year and 16,000 people dying from it. Although survival rates have improved over time, they continue to lag behind those attained by many economic neighbours[1] and so developing educational interventions to improve outcomes is a priority.

Some potential explanations for these survival differences include variability in the quality of care and access to services. For example, local recurrence and survival rates in rectal cancer are related to the quality of the surgical resection[2] so improving surgical quality is likely to improve outcomes. Likewise, ensuring gold standard diagnostic, staging and multidisciplinary care across all aspects of the patient pathway have a demonstrable impact on outcomes[3] while screening for Lynch syndrome and deficient mismatch repair will enable more effective management of patients.

Other countries have acknowledged these relationships and taken steps to improve standards. For instance, in the early 1990s, Norway recognised there was huge variation in local recurrence rates depending on which surgeon operated[4]. In response, they initiated a training programme to quantify variation and improve the quality of surgery. This strategy was a success, reducing local recurrence and improving overall survival[5]. As a result similar programmes in other countries, including the UK were established with equally positive outcomes including lower postoperative mortality[6] and better survival[3, 7], lower permanent stoma[7] and local recurrence rates[8], better preoperative staging[9], improved selection of patients for non-surgical treatment[9] and the need for less emergency surgery[3].

Whilst these programmes have undoubtedly had a positive impact, variations in management remain and particularly so in the UK. Here, although survival rates have improved, the gap to rates attained in comparable countries[10] have not closed. Better understanding of what is driving these variations will help to target educational interventions to improve care.

Yorkshire Cancer Research is a charity whose aim is to ensure that more people of Yorkshire and Humber avoid, survive and cope with cancer and, by 2025, they intend to have reduced cancer deaths in the region by 2,000 per year. As part of their strategy to achieve this they

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2  
3 have recently funded the Bowel Cancer Improvement Programme (YCR BCIP). This initiative  
4 builds upon the experience gained from several English National programmes [9, 11] and  
5 extends the approach of those successful programmes completed in Scandinavia [3, 8, 12].  
6  
7 It centres on the collection and analysis of robust colorectal cancer data to examine practice  
8 across the region, ensuring the multidisciplinary teams (MDTs) managing the disease engage  
9 with these data and agree areas for improvement. Educational interventions or other  
10 strategies can then be implemented to ensure optimal practice is achieved.  
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16 The aims of the YCR BCIP study are to:

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19 1. Quantify and report the variation in the demographics, management and outcomes  
20 of the region's colorectal cancer patients using  
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22 a. routinely collected clinical datasets,  
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24 b. new information on aspects of care not currently quantifiable through  
25 existing datasets (e.g. Patient Reported Outcome Measures (PROMs), the  
26 molecular subtyping of the disease and the quality of radiology, pathology  
27 and surgery).  
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- 32 2. Where comparative data are available, to determine how outcomes from the  
33 Yorkshire and Humber region compare to the rest of England.  
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- 35 3. To provide the Yorkshire and Humber region colorectal MDTs with these data and,  
36 with their input, develop educational interventions to minimise any variation seen in  
37 order to optimise outcomes  
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- 40 4. Facilitate implementation of guidelines such as routine screening for Lynch  
41 syndrome and deficient mismatch repair status.  
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- 44 5. Evaluate improvement in outcomes over the study period.  
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## Methods and analysis

### Setting

The Yorkshire and Humber region of the UK has a population of approximately 5.7 million with around 3,300 colorectal cancer diagnoses a year, amounting to just over 10% of English diagnoses. Patients diagnosed with colorectal cancer in the region are managed by 16 different MDTs. These operate across 14 National Health Service (NHS) Trusts which provide health services for particular geographical areas of the region which exhibit a range of workloads, ranging between approximately 120-390 cases a year (4%-12% of the regional workload). Patients within the geographical areas covered by each Trust exhibit a variable range of demographic features such as socioeconomic deprivation and comorbidity [13].

### Programme Overview

YCR BCIP will interrogate routinely collected NHS data and, subject to patient consent, additional data collected specifically for the programme. Baseline performance outcomes for each MDT from across the region will be assessed. The knowledge will be fed back to each MDT and a programme of educational interventions developed based on the performance outcomes. The process will be iterative as outlined in Figure 1. The programme will run from 1<sup>st</sup> April 2016 until 31 March 2021.

Following a regional meeting of MDT representatives to discuss, plan and agree to programme participation held in June 2016, six specialty groups were initially established. The remit of these groups is to provide oversight and direction for their clinical specialty within the programme, to review data and analyses and to develop appropriate educational initiatives. The six groups focused on the main clinical disciplines involved in the MDT; surgery, radiology, pathology, clinical oncology, medical oncology, and specialist nursing. Group membership was drawn from all of the region's MDTs and an individual established from each to act as a coordinator between the research team and MDT. The need for a separate anaesthetics workstream was subsequently identified and introduced.

### Study Cohort/Participants

Although broad ranging, it was recognised that the routine colorectal cancer data available is not sufficient to quantify all aspects of care robustly. Whilst routine data provides good information available on 'hard' outcomes such as which operation was undertaken or

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3 survival time, there is a lack of information on what this really means to the individual  
4 concerned and the quality of that survival. This precludes the production of the rich  
5 intelligence the MDTs want to fully understand variation in care. Therefore data collated in  
6 YCR BCIP will come from three main sources:  
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#### 9 10 ***Existing population-based datasets***

11  
12 Consisting of routine NHS datasets providing both regional data (around 3,300 cases per  
13 year) and comparative national data (around 28,700 cases per year) on patient and tumour  
14 characteristics, treatment choices, diagnosis pathways and patient outcomes.  
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#### 17 18 ***Direct PROMs and tissue collection***

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20 Consisting of regional PROMs data collected directly from patients on health-related quality  
21 of life (at both the time of diagnosis, before primary treatment if possible and again at 12  
22 months post diagnosis) and molecular testing of tumour and tumour-associated normal  
23 mucosal tissue samples.  
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27 All MDTs in the region have been invited to participate in this element of the YCR BCIP.  
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29 Every colorectal cancer patient (ICD10 C18-C20) is eligible if they are considered suitable for  
30 treatment, English language literate, aged at least 18 years old and with capacity to give  
31 informed consent. Participants will be asked to consent to the study prior to  
32 commencement of primary treatment or following an emergency intervention.  
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#### 35 36 ***Audit and survey data***

37  
38 Consisting of unlinked anonymised data collected from regional MDTs in the form of an  
39 audit (specimen photographs or scans for example) or a clinician survey. The exact nature of  
40 these shall be identified by each clinical discipline depending on the needs and availability of  
41 existing data.  
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#### 45 46 **Cohort Identification and Patient Recruitment**

##### 47 48 ***Existing population-based datasets***

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50 All patients diagnosed with a first primary colorectal cancer (ICD10 C18-C20) in England  
51 from 1<sup>st</sup> January 2005 until the end of the study will be obtained from the National Cancer  
52 Registration and Analysis Service (NCRAS) [14] and assigned a managing MDT.  
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##### 55 56 ***Direct PROMs and tissue collection***

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58 This research project is adopted by the NIHR Yorkshire and Humber Clinical Research  
59 Network and therefore recruitment will be undertaken across the region by network  
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3 research and clinical staff working collaboratively. Recruitment will run over a 30 month  
4 period.  
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7 Eligible patients will be identified and approached in two ways.

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9 1. Identified via the MDT and informed about the study by consultant letter sent  
10 out with their appointment letter for the primary pre-assessment clinic visit . Where  
11 possible, patients will be approached about the study at this clinic appointment. Patients  
12 missed at this appointment will be contacted at the earliest convenient time point and  
13 informed about the study.  
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15 2. Identified by their NHS clinical team if they present as an acute admission (for example  
16 with a bowel obstruction) and informed about the study by their clinical team following the  
17 emergency intervention (e.g. surgery).  
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#### 20 21 22 ***Audit and survey data***

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24 No specific recruitment will be performed for these data as only anonymised data used as  
25 part of routine patient care will be used. Regional MDT clinicians will be invited to complete  
26 online surveys.  
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#### 29 30 31 **Consent**

##### 32 33 ***Existing population-based datasets***

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35 The data is derived from patient-level information collected by the NHS, as part of the care  
36 and support of cancer patients. NCRAS has specific legal permission to collect this  
37 information without the need to seek consent, however, patients can ask NCRAS to remove  
38 their details from the cancer registry at any time.  
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##### 40 41 42 ***Direct PROMs and tissue collection***

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44 Identified patients will be provided with full study information (written and verbal) by  
45 specialist research nurses or Clinical Nurse Specialists who have undergone Good Clinical  
46 Practice (GCP training) to assure the rights, safety and wellbeing of research participants are  
47 protected ([https://www.nihr.ac.uk/our-research-community/clinical-research-  
48 staff/learning-and-development/national-directory/good-clinical-practice/](https://www.nihr.ac.uk/our-research-community/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/)). Written  
49 consent may be taken at the time of this approach but patients will be given up to a week  
50 to think about study participation. Patients who wish to join the study will be asked to read,  
51 complete and sign a consent form, including their contact details name, address and/or  
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3 email address. The person taking consent will also record the patient's date of birth, NHS  
4 number and gender.  
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6 Patients are asked to consent to their clinical team being informed in the event that  
7 clinically relevant laboratory results are found. This includes the possibility of hereditary  
8 conditions identified through tumour testing e.g. Lynch syndrome or deficient mismatch  
9 repair status. These will be confirmed through routine NHS Clinical Genetics testing after  
10 counselling following referral from the local clinical teams with no germline testing taking  
11 place through the programme.  
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### 17 ***Audit and survey data***

18 No specific consent will be needed for these data as only anonymised data used as part of  
19 routine patient care will be used.  
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### 23 **Data Collection**

#### 24 ***Existing population-based datasets***

25 The YCR BCIP seeks to make maximum use of routine NHS datasets and these are brought  
26 together in the UK Bowel Cancer Intelligence Hub[15] where data from the NCRAS are linked  
27 to other datasets relevant to colorectal cancer to provide the richest data possible and  
28 enable analysis of the full cancer pathway. These include, but are not limited to: Hospital  
29 Episode Statistics, Radiotherapy Dataset, Systematic Anti-Cancer Therapy Dataset and  
30 Routes to Diagnosis. This data will cover ten years preceding the start of the programme to  
31 provide a baseline and be routinely updated to assess changes throughout it.  
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#### 40 ***Direct PROMs and tissue collection***

41 Participants will have the option of completing the PROMs either online (ePROMs) using the  
42 University of Leeds secure questionnaire administration system QTool [16], accessed via the  
43 study website, ([www.YCRBCIP.leeds.ac.uk](http://www.YCRBCIP.leeds.ac.uk)) or on paper (pPROMs) with a pre-paid return  
44 envelope. They will be asked to complete the survey as soon as possible after consenting.  
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49 This may be completed while attending hospital at the time of consent or later at home. Just  
50 prior to the 12 month follow-up questionnaire the patient status will be checked via NCRAS  
51 to confirm that the patient is still alive. Patients will then be sent an email/letter 12 months  
52 post-diagnosis by the YCR BCIP research team, inviting them to complete PROMs again (on  
53 paper or online according to patient preference). At both time points reminder letters or  
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3 emails will be sent at two weeks and followed up two weeks later (if no response) with the  
4 survey being resent with the reminder letter. The process is outlined in Figure 2.  
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7 The tissue samples to be collected for this study are:

- 8 1. excess pre-treatment, diagnostic biopsy tumour tissue
- 9 2. excess tissue following surgical resection (tumour and tumour-associated normal  
10 mucosal tissue)
- 11 3. excess tumour tissue following the biopsy or resection of distant metastases  
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16 The tissue samples will be formalin-fixed and paraffin wax-embedded as per the routine  
17 histopathology procedures at the patients' hospital. Tissue blocks will be used for any  
18 routine clinical diagnostic procedures required by the hospital before being sent to  
19 Pathology at the University of Leeds, and will be available to return to the hospital for  
20 further clinical testing if required.  
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#### 25 ***Audit and survey data***

26 No additional patient-level data collection beyond that as part of routine patient care will be  
27 performed. Clinicians at regional MDTs will complete surveys anonymously online using  
28 [www.onlinesurveys.ac.uk](http://www.onlinesurveys.ac.uk) (formally Bristol Online Survey).  
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#### 33 **Data Linkage**

34 Whilst initially the existing population datasets and direct PROMs and tissue collection will  
35 be analysed separately, these will subsequently be linked together through the UK  
36 Bowel Cancer Intelligence Hub. This will provide additional patient characteristics for  
37 analysis of the PROMs and tissue data.  
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#### 43 **Data analysis**

##### 44 ***Existing population-based datasets***

45 Baseline assessments of care in the region are to be performed on individuals diagnosed  
46 with colorectal cancer (ICD10 C18-C20) in Yorkshire and Humber, enabling comparison  
47 between teams in the region and with national data[13]. Initially this includes using  
48 descriptive analysis and statistical methods such as regression modelling, survival analysis  
49 and funnel plots [17] comparing the following data: demographic characteristics, tumour  
50 characteristics, surgery and oncology management and short and long-term outcomes.  
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3 Some analyses will be rerun periodically over the course of the programme to evaluate the  
4 impact on outcomes of specific educational interventions. The measures to be analysed and  
5 the sources of these can be found in Table 1.  
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### 8 ***Direct PROMs and tissue collection***

9  
10 Participants will be asked to complete a range of validated generic, cancer-specific and  
11 colorectal cancer-specific PROMs in addition to socio-demographic characteristics. Content  
12 has been informed by: clinical relevance, opinion of service users, overall length and  
13 participant burden[18], reviews of questionnaires measuring quality of life in colorectal  
14 cancer patients[19-23] and UK recommendations for the core outcomes set for trials in  
15 colorectal cancer surgery[24].  
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18 The survey comprises four sections at baseline and five sections at follow-up. The same  
19 PROMs are included at both time points. In addition, at the second time point (12-months  
20 post diagnosis) participants will be asked to complete questions about the financial costs of  
21 cancer. The time taken to complete the survey is estimated is about 30-35 minutes.  
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#### 24 *Section One: Your overall health and quality of life (both time points)*

- 25 • European Organisation for Research and Treatment of Cancer (EORTC) Quality of  
26 Life Questionnaire QLQ-C30, the colorectal cancer specific module and items from  
27 the prostate, endometrial and cervical cancer modules [25-29]
- 28 • EuroQol Group EQ-5D-5L [30]

#### 29 *Section Two: Your everyday life and well-being (both time points)*

- 30 • Social Difficulties Inventory (SDI-21) [31, 32]
- 31 • The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [33, 34]

#### 32 *Section Three: Managing your health (both time points)*

- 33 • Self-efficacy for Managing Chronic Disease [35]
- 34 • The Brief Illness Perceptions Questionnaire (B-IPQ) [36]

#### 35 *Section Four: The financial cost of cancer (Time 2 only)*

- 36 • A questionnaire developed in-house based on one used in the ePOCS study[37].

#### 37 *Section Four: Questions about you (Time 1) and Section Five: Questions about you (Time 2)*

38 Self-report socio-demographic and clinical details

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40 Descriptive statistics will be used to report the survey results and assess the quality of life  
41 outcomes of the participants. Following data linkage, the outcomes will be analysed  
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3 according to stage of disease, treatment type, comorbidity, age, ethnic and  
4 sociodemographic group (and other relevant variables). These descriptive analyses will  
5 identify potential relationships of interest which can be investigated further. Regression  
6 modelling will be used to investigate associations amongst the different types of variables to  
7 identify statistically and clinically significant risk factors and predictors of outcomes. In order  
8 to be robust, analyses will require appropriate adjustment for case-mix and other  
9 confounding factors and may require more complex techniques, such as the modelling of  
10 hierarchies within the data (multilevel modelling), post-hoc weighting to overcome response  
11 bias and multiple imputation of missing data.  
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16 Based on the number of diagnoses per year, there is potential to consent approximately  
17 8,250 patients from sites across the region over a 30 month recruitment period. However  
18 due to eligibility restrictions, consent by MDT and by individuals, administrative/practical  
19 issues and staggered site recruitment start dates, the participation rate is likely to be less.  
20 Using estimates based on previous studies [38, 39] the consent rate is estimated to be  
21 around 42% and the an attrition rate of approximately 35% at the 12 months follow-up  
22 point, giving a sample size of at least 1200. This will provide MDTs with a comprehensive  
23 descriptive profile of their patients in terms of quality of life outcomes; more complex  
24 analyses will be undertaken if sufficient numbers are accrued.  
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28 Tissue samples removed at surgery or biopsy which are surplus to routine clinical  
29 requirements will be utilised by the research team for upfront testing of novel biomarkers.  
30 YCR BCIP will test for novel or rare potentially treatable targets via a range of molecular  
31 techniques. The immunohistochemical markers of interest include, HER2, PTEN, PD-1 and  
32 PD-L1, amphiregulin and epiregulin, and immune system markers CD3 and CD8. The study  
33 will also undertake phenotype analysis by using high-resolution scanned images of tumours  
34 using novel algorithms to identify improved prognostic and predictive markers of outcome.  
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38 Next Generation Sequencing and/or pyrosequencing will be performed on any extracted  
39 DNA to identify tumours with specific gene hotspot mutations including, KRAS, NRAS, BRAF,  
40 EGFR and PIK3CA. Other molecular markers linked to causation, outcome and response to  
41 therapy will also be investigated e.g. bacterial toxin carriage or fusobacterium nucleatum.  
42 Analysis of RNA expression levels of receptor ligands such as amphiregulin and epiregulin,  
43 and HER2 and HER3 may also be performed.  
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### ***Audit and survey data***

The analyses of audit and survey data will be dependent clinical specialities involved and the nature of the data collected.

### **Data Safeguards**

Participant recruitment will be undertaken by each Trust involved in the study. Each research network site will allocate a study ID for potential participants. They will use a University of Leeds secure electronic transfer system every two weeks to inform the YCR BCIP research team of all recruitment activity. This will include the consented patients contact details, date of birth and NHS number to allow for follow-up and to ensure tissue blocks are appropriately labelled for tracking and data linkage. All subsequent participant contact will be undertaken by the central YCR BCIP team.

Storage of all hard copy documents will be in locked metal filing cabinets in research offices of the University of Leeds with secure access building controls. Tissue samples will be used and stored in a secure building with restricted access. Electronic data with pseudonymised (allocated ID number) patient information will be stored in a secure environment. These files will only be accessible to relevant members of the study analysis team. Where temporary storage of sensitive data is required (e.g. contact details for sending out repeat surveys), files will be accessible only to relevant members of the research team and not stored with any linked data. Members of the analysis team will not have access to any identifiable data. Hard copy data will be kept for 5 years following the end of the study (until 2026) for long term follow-up.

### **Development of Educational Interventions**

The analyses will be disseminated and discussed by regional MDTs at events for each clinical discipline. Agreements of educational needs to improve care will be agreed along with any additional data capture and audit processes that teams agree are required. The process is repeated with ongoing data analyses to establish the improvements in management and outcomes that have occurred (Figure 1). As YCR BCIP progresses, further work will be undertaken looking at other outcomes including, but not limited to, those related to screening, pathology and long-term outcomes.

### **Public Patient Involvement**

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3 Patients and carers were actively engaged through the PROMS Working Group to develop  
4 the design and content of the patient questionnaires, the patient information sheet and  
5 consent form. At the request of the patients and carers, additional questions were included  
6 around the financial impact of cancer and a specific request was made to EORTC to amend  
7 the EORTC colorectal module and add specific questions from other EORTC modules to  
8 understand side effects of cancer and cancer treatments. EORTC granted these specific  
9 amendments for this study. The electronic and paper copies of the final draft  
10 questionnaires were tested with patients attending a colorectal cancer follow-up clinic at  
11 one of the region hospitals. Modification to the layout of the questionnaires were made  
12 following the results of the testing. The testing gave an understanding of the length of time  
13 it took patients to complete the questionnaires. The PROMS Working Group will remain  
14 active throughout the length of the study; the group will be kept apprised of recruitment  
15 levels and early results. It is expected that the patients will advise on the analysis and how  
16 the results are communicated to the regional clinical teams and wider audiences.  
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## 31 Discussion

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33 The YCR BCIP study ambitiously aims to improve outcomes for patients with colorectal  
34 cancer across the Yorkshire and Humber region by in-depth analysis of existing and newly  
35 captured data, and by actively engaging local MDTs. In its initial stages, this will be done by  
36 demonstrating the variation in the demographics, management and outcomes in the region  
37 using routine NHS datasets. However, given the limitations of what can be achieved with  
38 existing data, the YCR BCIP is collecting additional data to analyse alongside this with the  
39 purpose to better understand what is driving the observed variation.  
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46 The PROMs data will enrich other study data and allow for an 'in-depth' description of what  
47 life is really like for colorectal cancer patients at diagnosis and a year later. At present, the  
48 patient voice is not 'measured' routinely as part of clinical practice, neglecting the impact of  
49 illness and treatment on the everyday lives of patients. YCR BCIP will change this with the  
50 integration of PROMs administration into clinical practice[39]. The PROMs used in this study  
51 have been selected with input from experts in colorectal cancer and psychosocial care:  
52 patients, clinical nurse specialists and doctors. Although the length of the survey would not  
53 be feasible to administer in everyday practice, information on which PROMs provide the  
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3 most meaningful data will be obtained. In the future risk-stratified follow-up may  
4 incorporate not only clinical indicators but also key quality of life indicators to inform best  
5 supportive care[40].  
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9 Results from the tissue collection and testing could impact on treatment and follow-up  
10 decisions for the participating patients and, potentially, their families. For example, the  
11 results may indicate that a patient could benefit from a targeted treatment being tested  
12 through an open clinical trial if they develop an indication for further treatment e.g. Medical  
13 Research Council FOCUS4 [41]. Increased risks of having a hereditary condition may be  
14 identified, which not only has implications for the patient but also their family.  
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## 20 **Ethics and dissemination**

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23 The study was granted ethical approval (17/WM/0374) by the West Midlands – Solihull  
24 Research Ethics Committee in December 2017. The study was approved by the Health  
25 Research Authority and granted approval for inclusion in the National Institute for Health  
26 Research’s portfolio of studies in December 2017 (Project ID 227673).  
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31 The YCR BCIP is offering a novel approach to address the variation in colorectal cancer care  
32 across a large region of the UK. Engagement of the region’s MDTs with their data will lead to  
33 a range of educational initiatives, studies and clinical audits that aim to optimise practice  
34 across the region. It is planned that the outcomes of these will be presented to the relevant  
35 specialty group for review and to develop actions based on findings. Further work from the  
36 seven specialty groups involved in the programme: surgery, radiology, pathology, clinical  
37 oncology, medical oncology, nursing and anaesthetics, will be reported soon.  
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## 47 **Authors’ contributions**

48 PQ is the principal investigator. NW, PW and EM are coinvestigators and/or workstream  
49 leads. Together these authors conceived and designed the study. HR and JM manage the  
50 study. JT provides statistical support. AG provides pathology support. All authors  
51 contributed to writing of the manuscript and have approved a final version.  
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## 56 **Competing interests**

57  
58 The authors declare that they have no competing interests.  
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### Figure Legends

Figure 1: Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCRBCIP) process and study design.

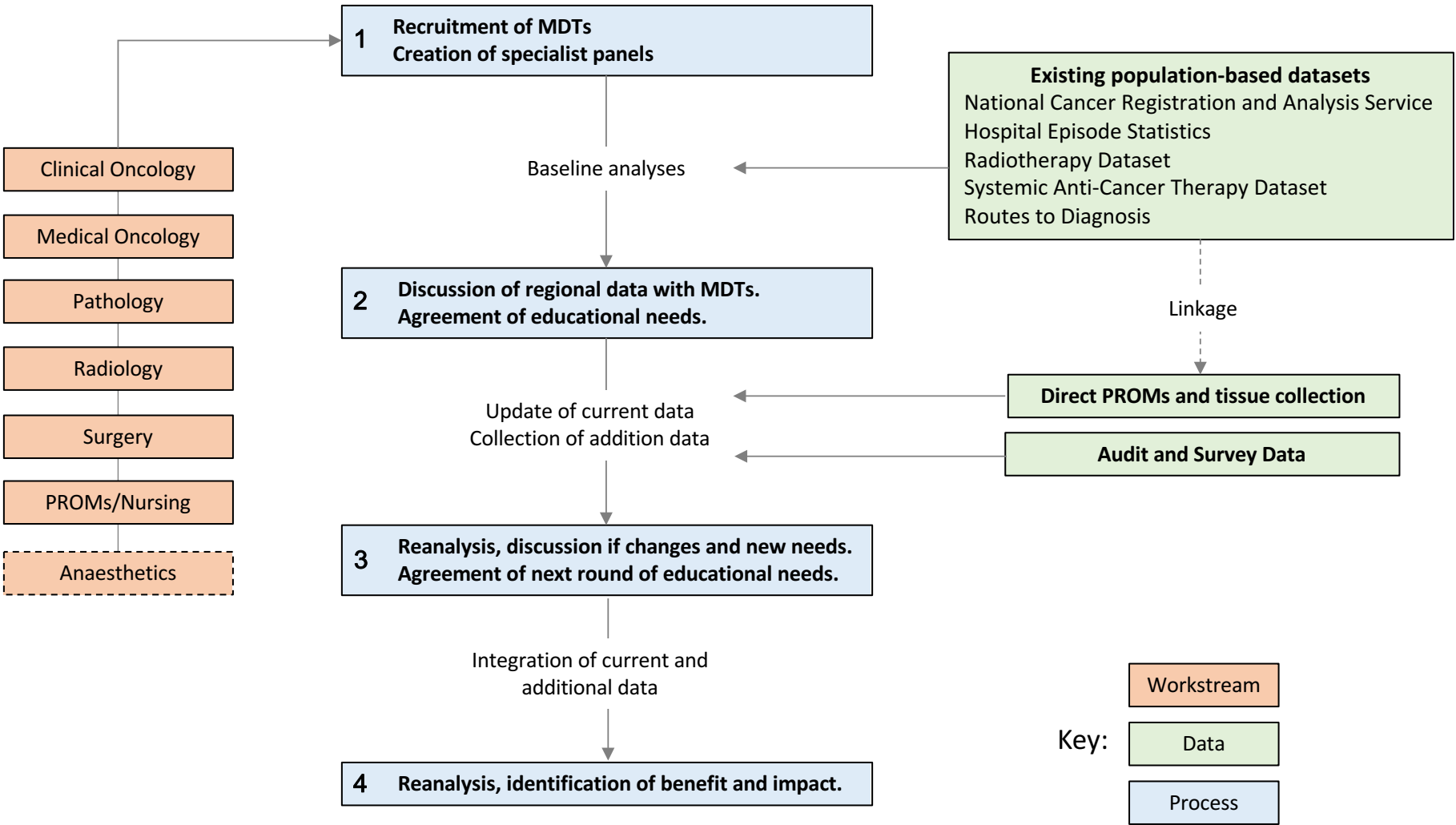
Figure 2: Process for the Patient Reported Outcomes Measures (PROMs) study.

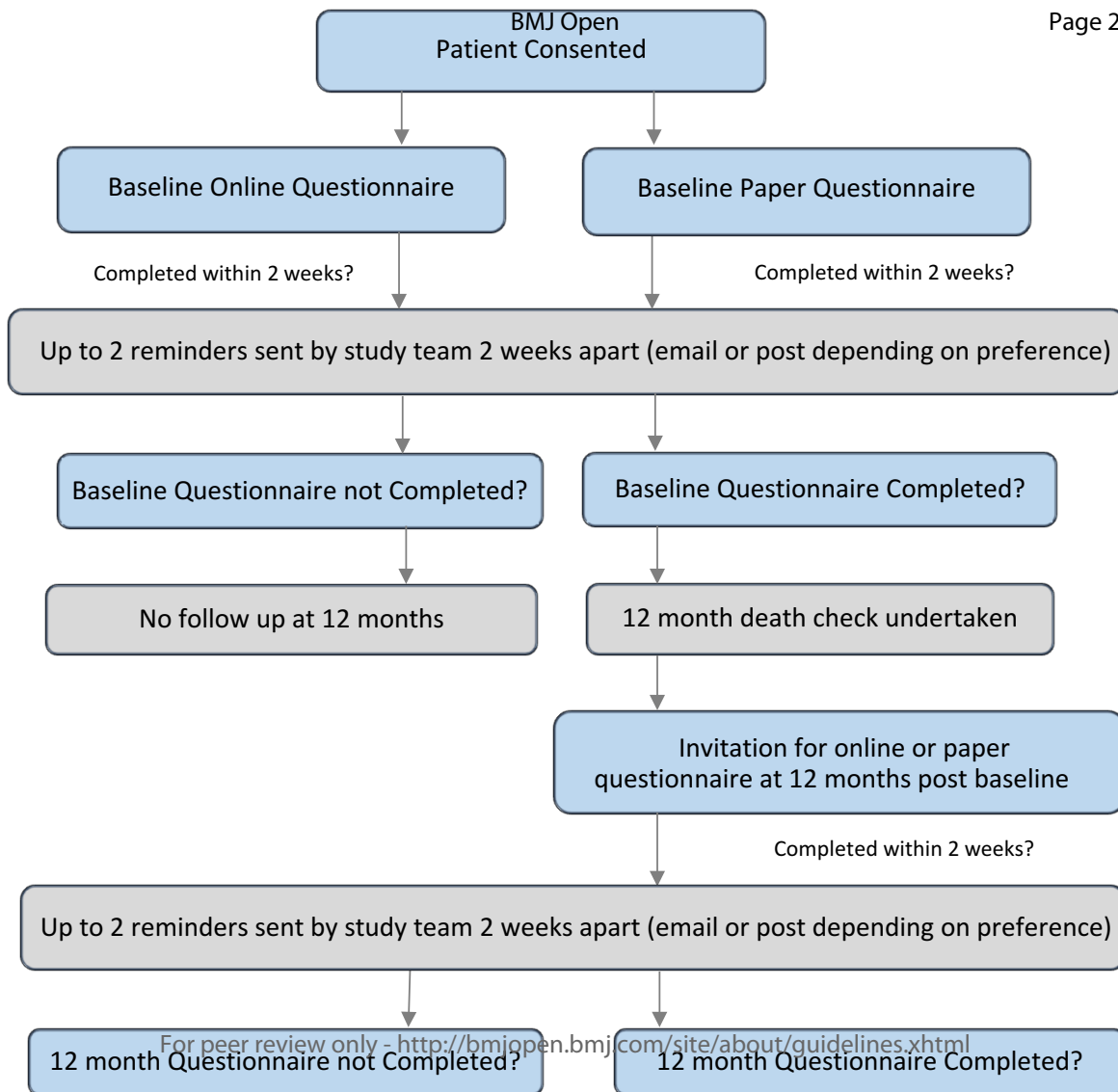
	Data Source		
	Existing population-based datasets	Direct PROMs and tissue collection	Audit and survey data
<b>Patient and Tumour Characteristics</b>			
Age & sex	Yes (NCRAS)	Yes	
Ethnicity	Yes (NCRAS)	Yes	
Height & Weight		Yes	
Comorbidity	Yes (NCRAS)	Yes	
Socio-economic status	Yes (NCRAS)	Yes	
Stage & site	Yes (NCRAS)		
Method of admission	Yes (RtD)		
<b>Treatment Variation</b>			
Surgical resection rate	Yes (HES)		
Quality of surgery			Yes
Abdominoperineal excision rate	Yes (HES)		
Use of adjuvant & palliative chemotherapy	Yes (SACT)		Yes
Use of neoadjuvant radiotherapy	Yes (RTDS)		
Use of laparoscopic surgery	Yes (HES)		
Emergency care procedures	Yes (HES)		Yes
Practice of anaesthetics			Yes
Quality of MRI reporting			Yes
Quality of CT imaging			Yes
Liver metastases resection rate	Yes (HES)		
Nodal yields and retrieval methods	Yes (NCRAS)		Yes
<b>Outcomes</b>			
30-day Postoperative mortality	Yes (NCRAS)		
1 to 5 year overall and net survival	Yes (NCRAS)		
18-month postoperative stoma rate	Yes (HES)		
Postoperative hospital stay	Yes (HES)		
Emergency readmission rates	Yes (HES)		
Overall health and quality of life		Yes	
Everyday life and well-being		Yes	
Self-efficacy for Managing Chronic Disease		Yes	
Financial cost of cancer		Yes	
Urinary function and faecal incontinence		Yes	
Sexual functioning		Yes	
Lower anterior resection syndrome		Yes	
Molecular subtyping		Yes	

Abbreviations: Magnetic resonance imaging (MRI), Computerized Tomography (CT), National Cancer Registration and Analysis Service (NCRAS), Routes to Diagnosis (RtD), Hospital Episode Statistics (HES), Systemic Anti-Cancer Therapy Dataset (SACT), Radiotherapy Dataset (RTDS).

**Table 1. Measures of patient characteristics, treatment measures and outcomes to analysed.**

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# BMJ Open

## A regional intensive multidisciplinary team intervention programme to improve colorectal cancer outcomes: study protocol for the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP)

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## **A regional intensive multidisciplinary team intervention programme to improve colorectal cancer outcomes: study protocol for the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP)**

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## Abstract

### Introduction

Although colorectal cancer outcomes in England are improving they remain poorer than many comparable countries. Yorkshire Cancer Research have, therefore, established a Bowel Cancer Improvement Programme (YCR BCIP) to improve colorectal cancer outcomes within Yorkshire and Humber, a region representative of the nation. It aims to do this by quantifying variation in practice, engaging with the colorectal multidisciplinary teams (MDTs) to understand this and instigating educational interventions to minimise it and improve outcomes.

### Methods and analysis

Initially, routine health datasets will be used to quantify variation in the demographics, management and outcomes of patients across the Yorkshire and Humber region and results presented to MDTs. The YCR BCIP is seeking to supplement these existing data with patient reported health-related quality of life information (PROMs) and tissue sample analysis. Specialty groups (surgery, radiology, pathology, clinical oncology, medical oncology, clinical nurse specialists and anaesthetics) have been established to provide oversight and direction for their clinical area within the programme, to review data and analysis and to develop appropriate educational initiatives.

### Ethics and dissemination

The YCR BCIP is seeking to address the variation in practice to significantly improve colorectal cancer outcomes across the Yorkshire and Humber region. PROMs and tissue sample collection and analysis will help to capture the information required to fully assess care in the region. Engagement of the region's MDTs with their data will lead to a range of educational initiatives, studies and clinical audits that aim to optimise practice across the region.

## Strengths and limitations of this study

- This study uses a novel approach by providing regional colorectal cancer MDTs with data and, with their input, develop educational interventions to minimise any variation seen in order to optimise outcomes.
- The strength of this study includes evaluating variation in the management and outcomes of colorectal cancer patients by combining routinely collected clinical datasets and novel information on aspects of care not currently quantifiable through existing datasets.
- The study will facilitate implementation of guidelines such as routine screening for Lynch syndrome and deficient mismatch repair status.
- The potential of the study is limited by the extent of engagement from regional colorectal cancer MDTs.

## Introduction

Colorectal cancer is a common disease in the UK with over 41,000 people diagnosed each year and 16,000 people dying from it. Although survival rates have improved over time, they continue to lag behind those attained by many economic neighbours<sup>1</sup> and so developing educational interventions to improve outcomes is a priority.

Some potential explanations for these survival differences include quality of care and access to services. For example, local recurrence and survival rates in rectal cancer are related to the quality of the surgical resection<sup>2</sup> so improving surgical quality is likely to improve outcomes. Likewise, ensuring gold standard diagnostic, staging and multidisciplinary care across all aspects of the patient pathway have a demonstrable impact on outcomes<sup>3</sup> while screening for Lynch syndrome and deficient mismatch repair will enable more effective management of patients.

Other countries have acknowledged these relationships and taken steps to improve standards. For instance, in the early 1990s, Norway recognised there was huge variation in local recurrence rates depending on which surgeon operated<sup>4</sup>. In response, they initiated a training programme to quantify variation and improve the quality of surgery. This strategy was a success, reducing local recurrence and improving overall survival<sup>5</sup>. As a result similar programmes in other countries, including the UK were established with equally positive outcomes including lower postoperative mortality<sup>6</sup> and better survival<sup>3 7</sup>, lower permanent stoma<sup>7</sup> and local recurrence rates<sup>8</sup>, better preoperative staging<sup>9</sup>, improved selection of patients for non-surgical treatment<sup>9</sup> and the need for less emergency surgery<sup>3</sup>.

Whilst these programmes have undoubtedly had a positive impact, variations in management remain and particularly so in the UK<sup>10 11</sup>. Although survival rates in the UK have improved, the gap to rates attained in comparable countries<sup>12</sup> have not closed. Better understanding of what is driving these variations will help to target educational interventions to improve care.

Yorkshire Cancer Research is a charity whose aim is to ensure that more people of Yorkshire and Humber “avoid, survive and cope” with cancer and, by 2025, they intend to have reduced cancer deaths in the region by 2,000 per year<sup>13</sup>. As part of their strategy to achieve this they have recently funded the Bowel Cancer Improvement Programme (YCR BCIP). This

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2  
3 initiative builds upon the experience gained from English National programmes<sup>9 14</sup> and  
4 extends the approach of those successful programmes completed in Scandinavia<sup>3 8 15</sup>. It  
5 centres on the collection and analysis of robust colorectal cancer data to examine practice  
6 across the region, ensuring the multidisciplinary teams (MDTs) managing the disease engage  
7 with these data and agree on areas for improvement. Educational interventions or other  
8 strategies can then be developed and implemented to ensure optimal practice is achieved.  
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14 This protocol paper gives an overview the YCR BCIP study, which has the following aims:

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17 1. Quantify and report the variation in the demographics, management and outcomes  
18 of the region's colorectal cancer patients using  
19  
20 a. routinely collected clinical datasets,  
21  
22 b. new information on aspects of care not currently quantifiable through  
23 existing datasets (e.g. Patient Reported Outcome Measures (PROMs), the  
24 molecular subtyping of the disease and the quality of radiology, pathology  
25 and surgery).  
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- 30 2. Determine how outcomes from the Yorkshire and Humber region compare to the  
31 rest of England.  
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- 33 3. Provide the Yorkshire and Humber region colorectal MDTs with these data and, with  
34 their input, develop educational interventions to minimise any variation seen in  
35 order to optimise outcomes  
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- 39 4. Facilitate implementation of guidelines such as routine screening for Lynch  
40 syndrome and deficient mismatch repair status.  
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- 43 5. Evaluate improvement in outcomes over the study period.  
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## Methods and analysis

### Setting

The Yorkshire and Humber region of the UK has a population of approximately 5.7 million with around 3,300 colorectal cancer diagnoses a year, amounting to just over 10% of English diagnoses. Patients diagnosed with colorectal cancer in the region are managed by 16 different MDTs. These operate across 14 National Health Service (NHS) Trusts which provide health services for particular geographical areas of the region which exhibit a range of workloads, ranging between approximately 120-390 cases a year (4%-12% of the regional workload). Patients within the geographical areas covered by each Trust exhibit a variable range of demographic features such as socioeconomic deprivation and comorbidity<sup>16</sup>.

### Programme Overview

YCR BCIP will examine routinely collected NHS data and, subject to patient consent, additional data collected specifically for the programme. Baseline performance outcomes for each MDT from across the region will be assessed. The knowledge will be fed back to each MDT and a programme of educational interventions developed based on the performance outcomes. The process will be iterative as outlined in Figure 1. The programme commenced on 1<sup>st</sup> April 2016 and will run until 31 March 2021.

Following a regional meeting of MDT representatives to discuss, plan and agree to programme participation held in June 2016, six specialty groups were initially established. The remit of these groups is to provide oversight and direction for their clinical specialty within the programme, to review data and analyses and to develop appropriate educational initiatives. The six groups focused on the main clinical disciplines involved in the MDT; surgery, radiology, pathology, clinical oncology, medical oncology, and specialist nursing. Group membership was drawn from all of the region's MDTs and an individual identified from each to act as a coordinator between the research team and MDT. The need for a separate anaesthetics workstream was subsequently identified and introduced. A lead clinician was also identified for each discipline, having the responsibility to coordinate educational events, gather opinion on best practice, formulate consensus views and drive agreed initiatives into routine clinical care across the region.

## Data Sources

Although broad ranging, it was recognised that the routine colorectal cancer data available is not sufficient to quantify all aspects of care robustly. Whilst routine data provides good information available on 'hard' outcomes such as which operation was undertaken or survival time, there is a lack of information on what this really means to the individual concerned and the quality of that survival. This precludes the production of the rich intelligence the MDTs want to fully understand variation in care. Therefore data collated in YCR BCIP will come from three main sources:

### ***Existing population-based datasets***

Consisting of routine NHS datasets providing both regional data (around 3,300 cases per year) and comparative national data (around 28,700 cases per year) on patient and tumour characteristics, treatment choices, diagnosis pathways and patient outcomes.

### ***Direct PROMs and tissue collection***

Consisting of regional PROMs data collected directly from patients on health-related quality of life (at both the time of diagnosis, before primary treatment if possible and again at 12 months post diagnosis) and molecular testing of tumour and tumour-associated normal mucosal tissue samples.

All MDTs in the region have been invited to participate in this element of the YCR BCIP. Every colorectal cancer patient (ICD10 C18-C20) is eligible if they are considered suitable for treatment, English language literate, aged at least 18 years old and with capacity to give informed consent. Participants will be asked to consent to the study prior to commencement of primary treatment or following an emergency intervention.

### ***Audit and survey data***

Consisting of unlinked anonymised data collected from clinicians at regional MDTs in the form of an audit (surgical specimen photographs or scans for example) or a clinician survey. The exact nature of these shall be identified by each clinical discipline depending on the needs and availability of existing data.

## Data collection

### ***Existing population-based datasets***

The YCR BCIP seeks to make maximum use of routine NHS datasets and these are brought together in the UK Bowel Cancer Intelligence Hub<sup>17</sup> where data from the NCRAS are linked

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2  
3 to other datasets relevant to colorectal cancer to provide the richest data possible and  
4 enable analysis of the full cancer pathway. These include, but are not limited to: Hospital  
5 Episode Statistics, Radiotherapy Dataset, Systematic Anti-Cancer Therapy Dataset and  
6 Routes to Diagnosis. This data will cover ten years preceding the start of the programme to  
7 provide a baseline and be routinely updated to assess changes throughout it.  
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11 All patients diagnosed with a first primary colorectal cancer (ICD10 C18-C20) in England  
12 from 1<sup>st</sup> January 2005 until the end of the study will be obtained from the National Cancer  
13 Registration and Analysis Service (NCRAS)<sup>18</sup> and assigned a managing MDT.  
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### 16 ***Direct PROMs and tissue collection***

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18 This research project is adopted by the NIHR Yorkshire and Humber Clinical Research  
19 Network and therefore recruitment will be undertaken across the region by network  
20 research and clinical staff working collaboratively. Recruitment will run over a 30 month  
21 period.  
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27 Eligible patients will be identified and approached in two ways.

- 28  
29 1. Identified via the MDT and informed about the study by consultant letter sent  
30 out with their appointment letter for the primary pre-assessment clinic visit . Where  
31 possible, patients will be approached about the study at this clinic appointment. Patients  
32 missed at this appointment will be contacted at the earliest convenient time point and  
33 informed about the study.  
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38 2. Identified by their NHS clinical team if they present as an acute admission (for example  
39 with a bowel obstruction) and informed about the study by their clinical team following the  
40 emergency intervention (e.g. surgery).  
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44 Participants will have the option of completing the PROMs either online (ePROMs) using the  
45 University of Leeds secure questionnaire administration system QTool<sup>19</sup>, accessed via the  
46 study website, ([www.YCRBCIP.leeds.ac.uk](http://www.YCRBCIP.leeds.ac.uk)) or on paper (pPROMs) with a pre-paid return  
47 envelope. They will be asked to complete the survey as soon as possible after consenting.  
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49 This may be completed while attending hospital at the time of consent or later at home. Just  
50 prior to the 12 month follow-up questionnaire the patient status will be checked via NCRAS  
51 to confirm that the patient is still alive. Patients will then be sent an email/letter 12 months  
52 post-diagnosis by the YCR BCIP research team, inviting them to complete PROMs again (on  
53 paper or online according to patient preference). At both time points reminder letters or  
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3 emails will be sent at two weeks and followed up two weeks later (if no response) with the  
4 survey being resent with the reminder letter. The process is outlined in Figure 2.  
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7 The tissue samples to be collected for this study are:

- 8 1. excess pre-treatment, diagnostic biopsy tumour tissue
- 9 2. excess tissue following surgical resection (tumour and tumour-associated normal  
10 mucosal tissue)
- 11 3. excess tumour tissue following the biopsy or resection of distant metastases

12 The tissue samples will be formalin-fixed and paraffin wax-embedded as per the routine  
13 histopathology procedures at the patients' hospital. Tissue blocks will be used for any  
14 routine clinical diagnostic procedures required by the hospital before being sent to  
15 Pathology at the University of Leeds, and will be available to return to the hospital for  
16 further clinical testing if required.  
17

18 Participants will be asked to complete a range of validated generic, cancer-specific and  
19 colorectal cancer-specific PROMs in addition to socio-demographic characteristics. Content  
20 has been informed by: clinical relevance, opinion of service users, overall length and  
21 participant burden<sup>20</sup>, reviews of questionnaires measuring quality of life in colorectal cancer  
22 patients<sup>21-25</sup> and UK recommendations for the core outcomes set for trials in colorectal  
23 cancer surgery<sup>26</sup>.  
24

25 The survey comprises four sections at baseline and five sections at follow-up. The same  
26 PROMs are included at both time points. In addition, at the second time point (12-months  
27 post diagnosis) participants will be asked to complete questions about the financial costs of  
28 cancer. The time taken to complete the survey is estimated is about 30-35 minutes.  
29

30 *Section One: Your overall health and quality of life (both time points)*

- 31 • European Organisation for Research and Treatment of Cancer (EORTC) Quality of  
32 Life Questionnaire QLQ-C30, the colorectal cancer specific module and items from  
33 the prostate, endometrial and cervical cancer modules <sup>27-31</sup>
- 34 • EuroQol Group EQ-5D-5L <sup>32</sup>

35 *Section Two: Your everyday life and well-being (both time points)*

- 36 • Social Difficulties Inventory (SDI-21) <sup>33 34</sup>
- 37 • The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) <sup>35 36</sup>

38 *Section Three: Managing your health (both time points)*



- Self-efficacy for Managing Chronic Disease <sup>37</sup>
- The Brief Illness Perceptions Questionnaire (B-IPQ) <sup>38</sup>

*Section Four: The financial cost of cancer (Time 2 only)*

- A questionnaire developed in-house based on one used in the ePOCS study<sup>39</sup>.

*Section Four: Questions about you (Time 1) and Section Five: Questions about you (Time 2)*

Self-report socio-demographic and clinical details

Based on the number of diagnoses per year, there is potential to consent approximately 8,250 patients from sites across the region over a 30 month recruitment period. However due to eligibility restrictions, consent by MDT and by individuals, administrative/practical issues and staggered site recruitment start dates, the participation rate is likely to be less. Using estimates based on previous studies <sup>40 41</sup> the consent rate is estimated to be around 42% and the an attrition rate of approximately 35% at the 12 months follow-up point, giving a sample size of at least 1200. This will provide MDTs with a comprehensive descriptive profile of their patients in terms of quality of life outcomes; more complex analyses will be undertaken if sufficient numbers are accrued.

***Audit and survey data***

No additional patient-level data collection beyond that as part of routine patient care will be performed. For example, anonymised MRI scans may be used as part of an educational training initiative but these have already been performed as part of the patient care pathway. Clinicians at regional MDTs will complete surveys anonymously online using [www.onlinesurveys.ac.uk](http://www.onlinesurveys.ac.uk) (formally Bristol Online Survey). No specific recruitment will be performed for these data as only anonymised data used as part of routine patient care will be used. Regional MDT clinicians will be invited to complete the online surveys via email and through speciality group meetings.

**Consent**

***Existing population-based datasets***

The data is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. NCRAS has specific legal permission to collect this information without the need to seek consent, however, patients can ask NCRAS to remove their details from the cancer registry at any time. Access to cancer registration data is controlled by the Public Health England Office for Data Release, and is only approved for

permitted medical purposes which include include: surveillance, clinical audit, service evaluation, ethically approved research, genetic counselling<sup>42</sup>.

### ***Direct PROMs and tissue collection***

Identified patients will be provided with full study information (written and verbal) by specialist research nurses or Clinical Nurse Specialists who have undergone Good Clinical Practice (GCP training) to assure the rights, safety and wellbeing of research participants are protected<sup>43</sup>. Written consent may be taken at the time of this approach but patients will be given up to a week to think about study participation. Patients who wish to join the study will be asked to read, complete and sign a consent form, including their contact details name, address and/or email address. The person taking consent will also record the patient's date of birth, NHS number and gender. Patients must consent to both PROMs participation and tissue collection to be included in the study.

Patients are asked to consent to their clinical team being informed in the event that clinically relevant laboratory results are found. This includes the possibility of hereditary conditions identified through tumour testing e.g. Lynch syndrome or deficient mismatch repair status. These will be confirmed through routine NHS Clinical Genetics testing after counselling following referral from the local clinical teams with no germline testing taking place through the programme.

### ***Audit and survey data***

No specific consent will be needed for these data as only anonymised data used as part of routine patient care will be used, for example specimen photographs or scans will have all identifiers removed.

### ***Data Linkage***

Whilst initially the existing population datasets and direct PROMs and tissue collection will be analysed separately, these will subsequently be linked together together through the UK Bowel Cancer Intelligence Hub using name, NHS number and date of birth. This will provide additional patient characteristics for analysis of the PROMs and tissue data.

### ***Analysis***

#### ***Existing population-based datasets***

Baseline assessments of care in the region are to be performed on individuals diagnosed with colorectal cancer (ICD10 C18-C20) in Yorkshire and Humber, enabling comparison

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3 between teams in the region and with national data<sup>16</sup>. Initially this includes using descriptive  
4 analysis and statistical methods such as regression modelling, survival analysis and funnel  
5 plots <sup>44</sup> comparing the following data: demographic characteristics, tumour characteristics,  
6 surgery and oncology management and short and long-term outcomes.  
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11 Some analyses will be rerun periodically over the course of the programme to evaluate the  
12 impact on outcomes of specific educational interventions. The measures to be analysed and  
13 the sources of these can be found in Table 1.  
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### 16 ***Direct PROMs and tissue collection***

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18 Descriptive statistics will be used to report the survey results and assess the quality of life  
19 outcomes of the participants. Following data linkage, the outcomes will be analysed  
20 according to stage of disease, treatment type, comorbidity, age, ethnic and  
21 sociodemographic group (and other relevant variables). These descriptive analyses will  
22 identify potential relationships of interest which can be investigated further. Regression  
23 modelling will be used to investigate associations amongst the different types of variables to  
24 identify statistically and clinically significant risk factors and predictors of outcomes. In order  
25 to be robust, analyses will require appropriate adjustment for case-mix and other  
26 confounding factors and may require more complex techniques, such as the modelling of  
27 hierarchies within the data (multilevel modelling), post-hoc weighting to overcome response  
28 bias and multiple imputation of missing data.  
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39 Tissue samples removed at surgery or biopsy which are surplus to routine clinical  
40 requirements will be utilised by the research team for upfront testing of novel biomarkers.  
41 YCR BCIP will test for novel or rare potentially treatable targets via a range of molecular  
42 techniques. The immunohistochemical markers of interest include, HER2, PTEN, PD-1 and  
43 PD-L1, amphiregulin and epiregulin, and immune system markers CD3 and CD8. The study  
44 will also undertake phenotype analysis by using high-resolution scanned images of tumours  
45 using novel algorithms to identify improved prognostic and predictive markers of outcome.  
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52 Next Generation Sequencing and/or pyrosequencing will be performed on any extracted  
53 DNA to identify tumours with specific gene hotspot mutations including, KRAS, NRAS, BRAF,  
54 EGFR and PIK3CA. Other molecular markers linked to causation, outcome and response to  
55 therapy will also be investigated e.g. bacterial toxin carriage or fusobacterium nucleatum.  
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3 Analysis of RNA expression levels of receptor ligands such as amphiregulin and epiregulin,  
4 and HER2 and HER3 may also be performed.

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7 Ultimately, the identification of treatable molecular markers will allow treatment to be  
8 targeted to specific tumour types in an effort to improve outcomes, benefitting future  
9 patients. Some participating patients may directly benefit from the study by being referred  
10 to a clinical trial, giving them the chance to receive tumour-specific treatment which is not  
11 routinely available.  
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### 15 16 ***Audit and survey data***

17 The analyses of audit and survey data will be dependent clinical specialities involved and  
18 the nature of the data collected. For example, the completion of MRI scans for rectal cancer  
19 at an educational training initiative would be assessed by agreement coefficients and results  
20 of surveys will be analysed using descriptive statistics.  
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### 25 26 **Data Safeguards**

27 Participant recruitment will be undertaken by each Trust involved in the study. Each  
28 research network site will allocate a study ID for potential participants. They will use a  
29 University of Leeds secure electronic transfer system every two weeks to inform the YCR  
30 BCIP research team of all recruitment activity. This will include the consented patients  
31 contact details, date of birth and NHS number to allow for follow-up and to ensure tissue  
32 blocks are appropriately labelled for tracking and data linkage. All subsequent participant  
33 contact will be undertaken by the central YCR BCIP team.  
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41 Storage of all hard copy documents will be in locked metal filing cabinets in research offices  
42 of the University of Leeds with secure access building controls. Tissue samples will be used  
43 and stored in a secure building with restricted access. Electronic data with pseudonymised  
44 (allocated ID number) patient information will be stored in a secure environment. These  
45 files will only be accessible to relevant members of the study analysis team. Where  
46 temporary storage of sensitive data is required (e.g. contact details for sending out repeat  
47 surveys), files will be accessible only to relevant members of the research team and not  
48 stored with any linked data. Members of the analysis team will not have access to any  
49 identifiable data. Hard copy data will be kept for 5 years following the end of the study (until  
50 2026) for long term follow-up.  
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### 59 60 **Development of Educational Interventions**

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3 The analyses will be disseminated and discussed by regional MDTs at events for each clinical  
4 discipline. Agreements of educational needs to improve care will be agreed along with any  
5 additional data capture and audit processes that teams agree are required. The process is  
6 repeated with ongoing data analyses to establish the improvements in management and  
7 outcomes that have occurred (Figure 1). As YCR BCIP progresses, further work will be  
8 undertaken looking at other outcomes including, but not limited to, those related to  
9 screening, pathology and long-term outcomes.

### 16 **Public Patient Involvement**

17 Patients and carers were actively engaged through the PROMS Working Group to develop  
18 the design and content of the patient questionnaires, the patient information sheet and  
19 consent form. At the request of the patients and carers, additional questions were included  
20 around the financial impact of cancer and a specific request was made to EORTC to amend  
21 the EORTC colorectal module and add specific questions from other EORTC modules to  
22 understand side effects of cancer and cancer treatments. EORTC granted these specific  
23 amendments for this study. The electronic and paper copies of the final draft  
24 questionnaires were tested with patients attending a colorectal cancer follow-up clinic at  
25 one of the region hospitals. Modification to the layout of the questionnaires were made  
26 following the results of the testing. The testing gave an understanding of the length of time  
27 it took patients to complete the questionnaires. The PROMS Working Group will remain  
28 active throughout the length of the study; the group will be kept apprised of recruitment  
29 levels and early results. It is expected that the patients will advise on the analysis and how  
30 the results are communicated to the regional clinical teams and wider audiences.

### 46 **Discussion**

47 The YCR BCIP study ambitiously aims to improve outcomes for patients with colorectal  
48 cancer across the Yorkshire and Humber region by in-depth analysis of existing and newly  
49 captured data, and by actively engaging local MDTs. In its initial stages, this will be done by  
50 demonstrating the variation in the demographics, management and outcomes in the region  
51 using routine NHS datasets. However, given the limitations of what can be achieved with  
52 existing data, the YCR BCIP is collecting additional data to analyse alongside this with the  
53 purpose to better understand what is driving the observed variation.

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2  
3 The PROMs data will enrich other study data and allow for an 'in-depth' description of what  
4 life is really like for colorectal cancer patients at diagnosis and a year later. At present, the  
5 patient voice is not 'measured' routinely as part of clinical practice, neglecting the impact of  
6 illness and treatment on the everyday lives of patients. YCR BCIP will change this with the  
7 integration of PROMs administration into clinical practice<sup>41</sup>. The PROMs used in this study  
8 have been selected with input from experts in colorectal cancer and psychosocial care:  
9 patients, clinical nurse specialists and doctors. Although the length of the survey would not  
10 be feasible to administer in everyday practice, information on which PROMs provide the  
11 most meaningful data will be obtained. In the future risk-stratified follow-up may  
12 incorporate not only clinical indicators but also key quality of life indicators to inform best  
13 supportive care<sup>45</sup>.

14  
15 Results from the tissue collection and testing could impact on treatment and follow-up  
16 decisions for the participating patients and, potentially, their families. For example, the  
17 results may indicate that a patient could benefit from a targeted treatment being tested  
18 through an open clinical trial if they develop an indication for further treatment e.g. Medical  
19 Research Council FOCUS4<sup>46</sup>. Increased risks of having a hereditary condition may be  
20 identified, which not only has implications for the patient but also their family.

21  
22 The YCR BCIP is offering a novel approach to address the variation in colorectal cancer care  
23 across a large region of the UK. Engagement of the region's MDTs with their data will lead to  
24 a range of educational initiatives, studies and clinical audits that aim to optimise practice  
25 across the region. It is planned that the outcomes of these will be presented to the relevant  
26 specialty group for review and to develop actions based on findings. The main limiting factor  
27 for the success of the study is that to understand the overall picture of colorectal cancer  
28 care and the ability to improve this in the region, relies on the extent of engagement from  
29 MDTs.

### 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 **Ethics and dissemination**

52  
53 The study was granted ethical approval (17/WM/0374) by the West Midlands – Solihull  
54 Research Ethics Committee in December 2017. The study was approved by the Health  
55 Research Authority and granted approval for inclusion in the National Institute for Health  
56 Research's portfolio of studies in December 2017 (Project ID 227673). Further work from  
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3 the seven specialty groups involved in the programme: surgery, radiology, pathology, clinical  
4 oncology, medical oncology, nursing and anaesthetics, will be reported as publications soon.  
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### 10 **Authors' contributions**

11 PQ is the principal investigator. NW, PW and EM are coinvestigators and/or workstream  
12 leads. Together these authors conceived and designed the study. HR and JM manage the  
13 study. JT provides statistical support. AG provides pathology support. All authors  
14 contributed to writing of the manuscript and have approved a final version.  
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### 19 **Competing interests**

20 The authors declare that they have no competing interests.  
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## Figure Legends

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Figure 1: Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCRBCIP) process and study design.

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3 Figure 2: Process for the Patient Reported Outcomes Measures (PROMs) study.  
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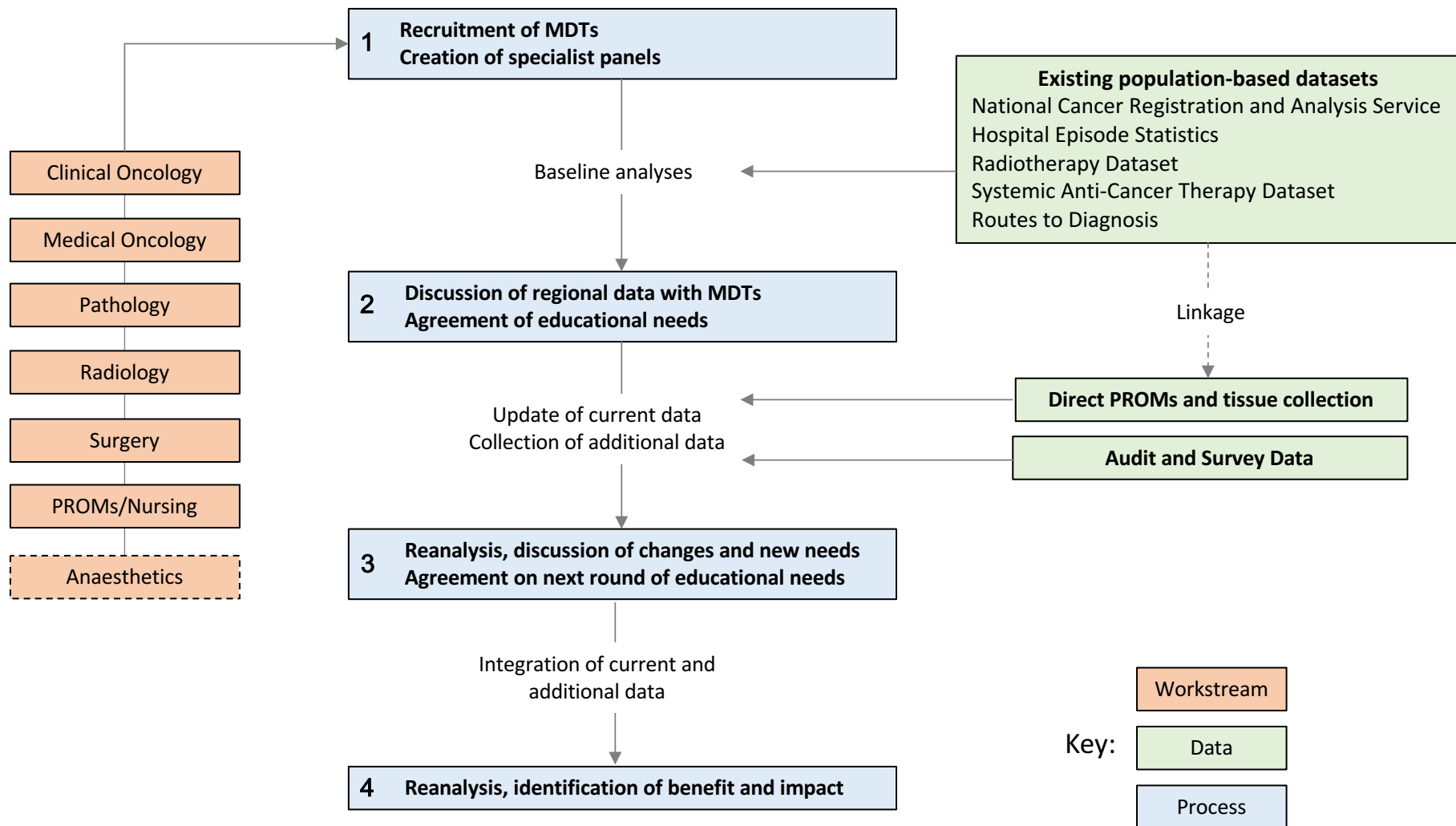
For peer review only

	Data Source		
	Existing population-based datasets	Direct PROMs and tissue collection	Audit and survey data
<b>Patient and Tumour Characteristics</b>			
Age & sex	Yes (NCRAS)	Yes	
Ethnicity	Yes (NCRAS)	Yes	
Height & Weight		Yes	
Comorbidity	Yes (NCRAS)	Yes	
Socio-economic status	Yes (NCRAS)	Yes	
Stage & site	Yes (NCRAS)		
Method of admission	Yes (RtD)		
<b>Treatment Variation</b>			
Surgical resection rate	Yes (HES)		
Quality of surgery			Yes
Abdominoperineal excision rate	Yes (HES)		
Use of adjuvant & palliative chemotherapy	Yes (SACT)		Yes
Use of neoadjuvant radiotherapy	Yes (RTDS)		
Use of laparoscopic surgery	Yes (HES)		
Emergency care procedures	Yes (HES)		Yes
Practice of anaesthetics			Yes
Quality of MRI reporting			Yes
Quality of CT imaging			Yes
Liver metastases resection rate	Yes (HES)		
Nodal yields and retrieval methods	Yes (NCRAS)		Yes
<b>Outcomes</b>			
30-day Postoperative mortality	Yes (NCRAS)		
1 to 5 year overall and net survival	Yes (NCRAS)		
18-month postoperative stoma rate	Yes (HES)		
Postoperative hospital stay	Yes (HES)		
Emergency readmission rates	Yes (HES)		
Overall health and quality of life		Yes	
Everyday life and well-being		Yes	
Self-efficacy for Managing Chronic Disease		Yes	
Financial cost of cancer		Yes	
Urinary function and faecal incontinence		Yes	
Sexual functioning		Yes	
Lower anterior resection syndrome		Yes	
Molecular subtyping		Yes	

Abbreviations: Magnetic resonance imaging (MRI), Computerized Tomography (CT), National Cancer Registration and Analysis Service (NCRAS), Routes to Diagnosis (RtD), Hospital Episode Statistics (HES), Systemic Anti-Cancer Therapy Dataset (SACT), Radiotherapy Dataset (RTDS).

**Table 1. Measures of patient characteristics, treatment measures and outcomes to analysed.**

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BMJ Open  
Patient Consented

Baseline Online Questionnaire

Baseline Paper Questionnaire

Completed within 2 weeks?

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

Baseline Questionnaire not Completed?

Baseline Questionnaire Completed?

No follow up at 12 months

12 month death check undertaken

Invitation for online or paper questionnaire at 12 months post baseline

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

12 month Questionnaire not Completed?

12 month Questionnaire Completed?

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# BMJ Open

## A regional multidisciplinary team intervention programme to improve colorectal cancer outcomes: study protocol for the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP)

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Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Gastrointestinal tumours < ONCOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

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## **A regional multidisciplinary team intervention programme to improve colorectal cancer outcomes: study protocol for the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP)**

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11 Quirke<sup>3</sup> on behalf of YCR BCIP Study Group.

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## Abstract

### Introduction

Although colorectal cancer outcomes in England are improving they remain poorer than many comparable countries. Yorkshire Cancer Research have, therefore, established a Bowel Cancer Improvement Programme (YCR BCIP) to improve colorectal cancer outcomes within Yorkshire and Humber, a region representative of the nation. It aims to do this by quantifying variation in practice, engaging with the colorectal multidisciplinary teams (MDTs) to understand this and developing educational interventions to minimise it and improve outcomes.

### Methods and analysis

Initially, routine health datasets will be used to quantify variation in the demographics, management and outcomes of patients across the Yorkshire and Humber region and results presented to MDTs. The YCR BCIP is seeking to supplement these existing data with patient reported health-related quality of life information (PROMs) and tissue sample analysis. Specialty groups (surgery, radiology, pathology, clinical oncology, medical oncology, clinical nurse specialists and anaesthetics) have been established to provide oversight and direction for their clinical area within the programme, to review data and analysis and to develop appropriate educational initiatives.

### Ethics and dissemination

The YCR BCIP is aiming to address the variation in practice to significantly improve colorectal cancer outcomes across the Yorkshire and Humber region. PROMs and tissue sample collection and analysis will help to capture the information required to fully assess care in the region. Engagement of the region's MDTs with their data will lead to a range of educational initiatives, studies and clinical audits that aim to optimise practice across the region.

## Strengths and limitations of this study

- This study uses a novel approach by providing regional colorectal cancer MDTs with data and, with their input, developing educational interventions to minimise any variation seen in order to optimise outcomes.
- The strength of this study includes evaluating variation in the management and outcomes of colorectal cancer patients by combining routinely collected clinical datasets and novel information on aspects of care not currently quantifiable through existing datasets.
- The study will facilitate implementation of guidelines such as routine screening for Lynch syndrome and deficient mismatch repair status.
- The potential of the study is limited by the extent of engagement from regional colorectal cancer MDTs.

## Introduction

Colorectal cancer is a common disease in the UK with over 41,000 people diagnosed each year and 16,000 people dying from it. Although survival rates have improved over time, they continue to lag behind those attained by many economic neighbours<sup>1</sup> and so developing educational interventions to improve outcomes is a priority.

Some potential explanations for these survival differences include quality of care and access to services. For example, local recurrence and survival rates in rectal cancer are related to the quality of the surgical resection<sup>2</sup> so improving surgical quality is likely to improve outcomes. Likewise, ensuring gold standard diagnostic, staging and multidisciplinary care across all aspects of the patient pathway have a demonstrable impact on outcomes<sup>3</sup> while screening for Lynch syndrome and deficient mismatch repair will enable more effective management of patients.

Other countries have acknowledged these relationships and taken steps to improve standards. For instance, in the early 1990s, Norway recognised there was huge variation in local recurrence rates depending on which surgeon operated<sup>4</sup>. In response, they initiated a training programme to quantify variation and improve the quality of surgery. This strategy was a success, reducing local recurrence and improving overall survival<sup>5</sup>. As a result similar programmes in other countries, including the UK were established with equally positive outcomes including lower postoperative mortality<sup>6</sup> and better survival<sup>3 7</sup>, lower permanent stoma<sup>7</sup> and local recurrence rates<sup>8</sup>, better preoperative staging<sup>9</sup>, improved selection of patients for non-surgical treatment<sup>9</sup> and the need for less emergency surgery<sup>3</sup>.

Whilst these programmes have undoubtedly had a positive impact, variations in management remain and particularly so in the UK<sup>10 11</sup>. Although survival rates in the UK have improved, the gap to rates attained in comparable countries<sup>12</sup> have not closed. A better understanding of what is driving these variations will help to target educational interventions to improve care.

Yorkshire Cancer Research is a charity whose aim is to ensure that more people of Yorkshire and Humber “avoid, survive and cope” with cancer and, by 2025, they intend to have reduced cancer deaths in the region by 2,000 per year<sup>13</sup>. As part of their strategy to achieve this they have recently funded the Bowel Cancer Improvement Programme (YCR BCIP). This

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3 initiative builds upon the experience gained from English National programmes<sup>9 14</sup> and  
4 extends the approach of those successful programmes completed in Scandinavia<sup>3 8 15</sup>. It  
5 centres on the collection and analysis of robust colorectal cancer data to examine practice  
6 across the region, ensuring the multidisciplinary teams (MDTs) managing the disease engage  
7 with these data and agree on areas for improvement. Educational interventions or other  
8 strategies can then be developed and implemented to ensure optimal practice is achieved.  
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12 This protocol paper gives an overview the YCR BCIP study, which has the following aims:  
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17 1. Quantify and report the variation in the demographics, management and outcomes  
18 of the region's colorectal cancer patients using  
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20 a. routinely collected clinical datasets,  
21  
22 b. new information on aspects of care not currently quantifiable through  
23 existing datasets (e.g. Patient Reported Outcome Measures (PROMs), the  
24 molecular subtyping of the disease and the quality of radiology, pathology  
25 and surgery).  
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29 2. Determine how outcomes from the Yorkshire and Humber region compare to the  
30 rest of England.  
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33 3. Provide the Yorkshire and Humber region colorectal MDTs with these data and, with  
34 their input, develop educational interventions to minimise any variation seen in  
35 order to optimise outcomes.  
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39 4. Facilitate implementation of guidelines such as routine screening for Lynch  
40 syndrome and deficient mismatch repair status.  
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44 5. Evaluate improvement in outcomes over the study period.  
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## Methods and analysis

### Setting

The Yorkshire and Humber region of the UK has a population of approximately 5.7 million with around 3,300 colorectal cancer diagnoses a year, amounting to just over 10% of diagnoses in England. Patients diagnosed with colorectal cancer in the region are managed by 16 different MDTs. These operate across 14 National Health Service (NHS) Trusts which provide health services for particular geographical areas of the region which exhibit a range of workloads, ranging between approximately 120-390 cases a year (4%-12% of the regional workload). Patients within the geographical areas covered by each Trust exhibit a variable range of demographic features such as socioeconomic deprivation and comorbidity<sup>16</sup>.

### Programme Overview

YCR BCIP will examine routinely collected NHS data and, subject to patient consent, additional data collected specifically for the programme. Baseline performance outcomes for each MDT from across the region will be assessed. The knowledge will be fed back to each MDT and a programme of educational interventions developed based on the performance outcomes. The process will be iterative as outlined in Figure 1. The programme commenced on 1<sup>st</sup> April 2016 and will run until 31 March 2021.

Following a regional meeting of MDT representatives to discuss, plan and agree to programme participation held in June 2016, six specialty groups were initially established. The remit of these groups is to provide oversight and direction for their clinical specialty within the programme, to review data and analyses and to develop appropriate educational initiatives. The six groups focused on the main clinical disciplines involved in the MDT; surgery, radiology, pathology, clinical oncology, medical oncology, and specialist nursing. Group membership was drawn from all of the region's MDTs and an individual identified from each to act as a coordinator between the research team and MDT. The need for a separate anaesthetics workstream was subsequently identified and introduced. A lead clinician was also identified for each discipline, having the responsibility to coordinate educational events, gather opinion on best practice, formulate consensus views and drive agreed initiatives into routine clinical care across the region.

## Data Sources

Although broad ranging, it was recognised that the routine colorectal cancer data available is not sufficient to quantify all aspects of care robustly. Whilst routine data provides good information available on 'hard' outcomes such as which operation was undertaken or survival time, there is a lack of information on what this really means to the individual concerned and the quality of that survival. This precludes the production of the rich intelligence the MDTs want to fully understand variation in care. Therefore data collated in YCR BCIP will come from three main sources:

### ***Existing population-based datasets***

Consisting of routine NHS datasets providing both regional data (around 3,300 cases per year) and comparative national data (around 28,700 cases per year) on patient and tumour characteristics, treatment choices, diagnosis pathways and patient outcomes. All patients diagnosed with a first primary colorectal cancer (ICD10 C18-C20) in England from 1<sup>st</sup> January 2005 until the end of the study and registered in the National Cancer Registration and Analysis Service (NCRAS)<sup>17</sup> will be eligible.

### ***Direct PROMs and tissue collection***

Consisting of regional PROMs data collected directly from patients via a questionnaire on health-related quality of life (at both the time of diagnosis, before primary treatment if possible and again at 12 months post diagnosis) and molecular testing of tumour and tumour-associated normal mucosal tissue samples.

All MDTs in the region have been invited to participate in this element of the YCR BCIP. Every colorectal cancer patient (ICD10 C18-C20) is eligible if they are considered suitable for treatment, English language literate, aged at least 18 years old and with capacity to give informed consent. Participants will be asked to consent to the study prior to commencement of primary treatment or following an emergency intervention.

### ***Audit and survey data***

Consisting of unlinked anonymised data collected from clinicians at regional MDTs in the form of an audit or a clinician survey. The exact nature of these shall be identified by each clinical discipline depending on the needs and availability of existing data. However, they are expected to include but are not limited to: an audit on surgical quality using specimen photographs, audits assessing the completeness in the recording of pathology and radiology reports, an audit on the methods of lymph node retrieval, and clinician surveys assessing the

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3 management of patients in the oncological, surgical and aeaethetics settings. All clinicians  
4 who are members of regional MDTs as part of the discipline being assessed will be eligible  
5 to participate.  
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## 8 9 **Data collection**

### 10 ***Existing population-based datasets***

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12 The YCR BCIP seeks to make maximum use of routine NHS datasets and these are brought  
13 together in the UK Colorectal Cancer Intelligence Hub<sup>18</sup> where data from the NCRAS are  
14 linked to other datasets relevant to colorectal cancer to provide the richest data possible  
15 and enable analysis of the full cancer pathway. These include, but are not limited to:  
16 Hospital Episode Statistics (HES), Radiotherapy Dataset, Systematic Anti-Cancer Therapy  
17 Dataset and Routes to Diagnosis. To provide a baseline, this data will cover the period from  
18 1<sup>st</sup> January 2005 until the start of the programme and be routinely collected until the end of  
19 the study to assess changes throughout it.  
20

21 All patients in the NCRAS data will be assigned a MDT using the HES procedure closest to the  
22 patient's diagnosis date. If no procedure is found, the closest inpatient or outpatient  
23 appointment to the diagnosis date at a hospital with a colorectal MDT is used. Those not  
24 assigned a MDT (<1% of patients) will be excluded from analyses. The assigned MDT will be  
25 assumed to have been responsible for the patient's management and treatment options.  
26

### 27 ***Direct PROMs and tissue collection***

28 This research project is adopted by the NIHR Yorkshire and Humber Clinical Research  
29 Network and therefore recruitment will be undertaken across the region by network  
30 research and clinical staff working collaboratively. Recruitment will run over a 30 month  
31 period.  
32

33 Eligible patients will be identified and approached in two ways.

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35 1. Identified via the MDT and informed about the study by consultant letter sent  
36 out with their appointment letter for the primary pre-assessment clinic visit . Where  
37 possible, patients will be approached about the study at this clinic appointment. Patients  
38 missed at this appointment will be contacted at the earliest convenient time point and  
39 informed about the study.  
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3 2. Identified by their NHS clinical team if they present as an acute admission (for example  
4 with a bowel obstruction) and informed about the study by their clinical team following the  
5 emergency intervention (e.g. surgery).  
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9 Participants will have the option of completing a PROMs questionnaire either online  
10 (ePROMs) using the University of Leeds secure questionnaire administration system QTool  
11 <sup>19</sup>, accessed via the study website, ([www.YCRBCIP.leeds.ac.uk](http://www.YCRBCIP.leeds.ac.uk)) or on paper (pPROMs) with a  
12 pre-paid return envelope. They will be asked to complete the questionnaire as soon as  
13 possible after consenting. This may be completed while attending hospital at the time of  
14 consent or later at home. Just prior to the 12 month follow-up questionnaire the patient  
15 status will be checked via NCRAS to confirm that the patient is still alive. Patients will then  
16 be sent an email/letter 12 months post-diagnosis by the YCR BCIP research team, inviting  
17 them to complete PROMs again (on paper or online according to patient preference). At  
18 both time points reminder letters or emails will be sent at two weeks and followed up two  
19 weeks later (if no response) with the questionnaire being resent with the reminder letter.  
20 The process is outlined in Figure 2.  
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24 Participants will be asked to complete a range of validated generic, cancer-specific and  
25 colorectal cancer-specific PROMs in addition to socio-demographic characteristics. Content  
26 has been informed by: clinical relevance, opinion of service users, overall length and  
27 participant burden<sup>20</sup>, reviews of questionnaires measuring quality of life in colorectal cancer  
28 patients<sup>21-25</sup> and UK recommendations for the core outcomes set for trials in colorectal  
29 cancer surgery<sup>26</sup>.  
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33 The questionnaire comprises four sections at baseline and five sections at follow-up. The  
34 questionnaire is estimated to take 30-35 minutes to complete.  
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38 *Your overall health and quality of life (both time points)*  
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- 40 • European Organisation for Research and Treatment of Cancer (EORTC) Quality of  
41 Life Questionnaire QLQ-C30, the colorectal cancer specific module and items from  
42 the prostate, endometrial and cervical cancer modules <sup>27-31</sup>
- 43 • EuroQol Group EQ-5D-5L <sup>32</sup>

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45 *Your everyday life and well-being (both time points)*  
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- 47 • Social Difficulties Inventory (SDI-21) <sup>33 34</sup>
- 48 • The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) <sup>35 36</sup>



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3 *Managing your health (both time points)*  
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- 5 • Self-efficacy for Managing Chronic Disease <sup>37</sup>
- 6 • The Brief Illness Perceptions Questionnaire (B-IPQ) <sup>38</sup>

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9 *Questions about you (both time points)*

- 10 • Self-reported socio-demographic and clinical details

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13 *The financial cost of cancer (second time point only)*

- 14 • A questionnaire developed in-house based on one used in the ePOCS study<sup>39</sup>.

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17 The tissue samples to be collected for this study are:

- 18 1. excess pre-treatment, diagnostic biopsy tumour tissue
- 19 2. excess tissue following surgical resection (tumour and tumour-associated normal  
20 mucosal tissue)
- 21 3. excess tumour tissue following the biopsy or resection of distant metastases

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The tissue samples will be formalin-fixed and paraffin wax-embedded as per the routine histopathology procedures at the patients' hospital. Tissue blocks will be used for any routine clinical diagnostic procedures required by the hospital before being sent to Pathology at the University of Leeds, and will be available to return to the hospital for further clinical testing if required.

Based on the number of diagnoses per year, there is potential to consent approximately 8,250 patients from sites across the region over a 30 month recruitment period. However due to eligibility restrictions, consent by MDT and by individuals, administrative/practical issues and staggered site recruitment start dates, the participation rate is likely to be less. Using estimates based on previous studies <sup>40 41</sup> the consent rate is estimated to be around 42% and the an attrition rate of approximately 35% at the 12 months follow-up point, giving a sample size of at least 1200. This will provide MDTs with a comprehensive descriptive profile of their patients in terms of quality of life outcomes; more complex analyses will be undertaken if sufficient numbers are accrued.

***Audit and survey data***

Audit data will be limited to data that are collected as part of routine patient care. For example, anonymised MRI scans that have been performed as a part of patient care may be used as part of an educational training initiative. No specific recruitment will be performed for these data as only anonymised data used as part of routine patient care will be used.

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3 Clinicians at regional MDTs will complete surveys anonymously online using  
4 [www.onlinesurveys.ac.uk](http://www.onlinesurveys.ac.uk) (formally Bristol Online Survey). These surveys will be used to  
5 assess clinical practice and patient management. For example, a survey regarding the use of  
6 adjuvant chemotherapy will be used to compare regional practice to the most recent  
7 evidence basis and used to inform a regional guideline for the treatment of these patients.  
8 Regional MDT clinicians will be invited to complete the online surveys via email and through  
9 speciality group meetings.  
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## 16 **Consent**

### 17 ***Existing population-based datasets***

18 The data is derived from patient-level information collected by the NHS, as part of the care  
19 and support of cancer patients. NCRAS has specific legal permission to collect this  
20 information without the need to seek consent, however, patients can ask NCRAS to remove  
21 their details from the cancer registry at any time. Access to cancer registration data and the  
22 other routine health datasets used in this study is controlled by the Public Health England  
23 (PHE) Office for Data Release, and is only approved for permitted medical purposes<sup>17</sup>. This  
24 work is covered by a data sharing contract with PHE (ODR1516\_369).  
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### 33 ***Direct PROMs and tissue collection***

34 Identified patients will be provided with full study information (written and verbal) by  
35 specialist research nurses or Clinical Nurse Specialists who have undergone Good Clinical  
36 Practice (GCP training) to assure the rights, safety and wellbeing of research participants are  
37 protected<sup>42</sup>. Written consent may be taken at the time of this approach but patients will be  
38 given up to a week to think about study participation. Patients who wish to join the study  
39 will be asked to read, complete and sign a consent form, including their contact details  
40 name, address and/or email address. The person taking consent will also record the  
41 patient's date of birth, NHS number and gender. Patients must consent to both PROMs  
42 participation and tissue collection to be included in the study.  
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50 Patients are asked to consent to their clinical team being informed in the event that  
51 clinically relevant laboratory results are found. This includes the possibility of hereditary  
52 conditions identified through tumour testing "e.g., Lynch syndrome or deficient mismatch  
53 repair status". These will be confirmed through routine NHS Clinical Genetics testing after  
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3 counselling following referral from the local clinical teams with no germline testing taking  
4 place through the programme.  
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### 6 ***Audit and survey data***

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8 No specific consent will be needed for these data as only anonymised data used as part of  
9 routine patient care will be used, for example specimen photographs or scans will have all  
10 identifiers removed. Consent for the surveys will be implied when the clinician completes a  
11 survey that they have been invited to.  
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### 16 **Data Linkage**

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18 Whilst initially the existing population datasets and direct PROMs and tissue collection will  
19 be analysed separately, these will subsequently be linked together through the UK  
20 Colorectal Cancer Intelligence Hub using name, NHS number and date of birth. This will  
21 provide additional patient characteristics for analysis of the PROMs and tissue data.  
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### 26 **Analysis**

#### 27 ***Existing population-based datasets***

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29 Baseline assessments of care in the region are to be performed on individuals diagnosed  
30 with colorectal cancer in Yorkshire and Humber, enabling comparison between teams in the  
31 region and with national data<sup>16</sup>. Initially this includes using descriptive analysis and  
32 statistical methods such as regression modelling, survival analysis and funnel plots<sup>43</sup>  
33 comparing the following data: demographic characteristics, tumour characteristics, surgery  
34 and oncology management and short and long-term outcomes.  
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41 Some analyses will be rerun periodically over the course of the programme to evaluate the  
42 impact on outcomes of specific educational interventions. The measures to be analysed and  
43 the sources of these can be found in Table 1.  
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#### 46 ***Direct PROMs and tissue collection***

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48 Descriptive statistics will be used to report the questionnaire results and assess the quality  
49 of life outcomes of the participants. Following data linkage, the outcomes will be analysed  
50 according to stage of disease, treatment type, comorbidity, age, ethnic and  
51 sociodemographic group (and other relevant variables). These descriptive analyses will  
52 identify potential relationships of interest which can be investigated further. Regression  
53 modelling will be used to investigate associations amongst the different types of variables to  
54 identify statistically and clinically significant risk factors and predictors of outcomes. In order  
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3 to be robust, analyses will require appropriate adjustment for case-mix and other  
4 confounding factors and may require more complex techniques, such as the modelling of  
5 hierarchies within the data (multilevel modelling), post-hoc weighting to overcome response  
6 bias and multiple imputation of missing data.  
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11 Tissue samples removed at surgery or biopsy which are surplus to routine clinical  
12 requirements will be utilised by the research team for upfront testing of novel biomarkers.  
13 YCR BCIP will test for novel or rare potentially treatable targets via a range of molecular  
14 techniques. The immunohistochemical markers of interest include, HER2, PTEN, PD-1 and  
15 PD-L1, amphiregulin and epiregulin, and immune system markers CD3 and CD8. The study  
16 will also undertake phenotype analysis by using high-resolution scanned images of tumours  
17 using novel algorithms to identify improved prognostic and predictive markers of outcome.  
18 Next Generation Sequencing and/or pyrosequencing will be performed on any extracted  
19 DNA to identify tumours with specific gene hotspot mutations including, KRAS, NRAS, BRAF,  
20 EGFR and PIK3CA. Other molecular markers linked to causation, outcome and response to  
21 therapy will also be investigated e.g. bacterial toxin carriage or fusobacterium nucleatum.  
22 Analysis of RNA expression levels of receptor ligands such as amphiregulin and epiregulin,  
23 and HER2 and HER3 may also be performed. The biomarkers will be linked to patient data  
24 (population-based and PROMs) and undergo regression modelling to identify associations to  
25 understand how tumour biology influences outcomes, response and quality of life and how  
26 tumour biology can be influenced by lifestyle.  
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#### 41 ***Audit and survey data***

42 The analyses of audit and survey data will be dependent clinical specialities involved and  
43 the nature of the data collected. For example, the completion of MRI scans for rectal cancer  
44 at an educational training initiative would be assessed by agreement coefficients and results  
45 of surveys will be analysed using descriptive statistics.  
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#### 50 **Data Safeguards**

51 Participant recruitment will be undertaken by each Trust involved in the study. Each  
52 research network site will allocate a study ID for potential participants. They will use a  
53 University of Leeds secure electronic transfer system every two weeks to inform the YCR  
54 BCIP research team of all recruitment activity. This will include the consented patients  
55 contact details, date of birth and NHS number to allow for follow-up and to ensure tissue  
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3 blocks are appropriately labelled for tracking and data linkage. All subsequent participant  
4 contact will be undertaken by the central YCR BCIP team.  
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7 Storage of all hard copy documents will be in locked metal filing cabinets in research offices  
8 of the University of Leeds with secure access building controls. Tissue samples will be used  
9 and stored in a secure building with restricted access. Electronic data with pseudonymised  
10 (allocated ID number) patient information will be stored in a secure environment. These  
11 files will only be accessible to relevant members of the study analysis team. Where  
12 temporary storage of sensitive data is required (e.g. contact details for sending out repeat  
13 questionnaires), files will be accessible only to relevant members of the research team and  
14 not stored with any linked data. Members of the analysis team will not have access to any  
15 identifiable data. Hard copy data will be kept for 5 years following the end of the study (until  
16 2026) for long term follow-up.  
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### 26 **Development of Educational Interventions**

27 The analyses will be disseminated and discussed by regional MDTs at events for each clinical  
28 discipline. Agreements of educational needs to improve care will be agreed along with any  
29 additional data capture and audit processes that teams agree are required. The process is  
30 repeated with ongoing data analyses to establish the improvements in management and  
31 outcomes that have occurred (Figure 1). As YCR BCIP progresses, further work will be  
32 undertaken looking at other outcomes including, but not limited to, those related to  
33 screening, pathology and long-term outcomes.  
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### 41 **Public Patient Involvement**

42 Patients and carers were actively engaged through the PROMS Working Group to develop  
43 the design and content of the patient questionnaires, the patient information sheet and  
44 consent form. At the request of the patients and carers, additional questions were included  
45 around the financial impact of cancer and a specific request was made to EORTC to amend  
46 the EORTC colorectal module and add specific questions from other EORTC modules to  
47 understand side effects of cancer and cancer treatments. EORTC granted these specific  
48 amendments for this study. The electronic and paper copies of the final draft  
49 questionnaires were tested with patients attending a colorectal cancer follow-up clinic at  
50 one of the region hospitals. Modification to the layout of the questionnaires were made  
51 following the results of the testing. The testing gave an understanding of the length of time  
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3 it took patients to complete the questionnaires. The PROMS Working Group will remain  
4 active throughout the length of the study; the group will be kept apprised of recruitment  
5 levels and early results. It is expected that the patients will advise on the analysis and how  
6 the results are communicated to the regional clinical teams and wider audiences.  
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## 10 11 12 **Discussion**

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15 The YCR BCIP study ambitiously aims to improve outcomes for patients with colorectal  
16 cancer across the Yorkshire and Humber region by in-depth analysis of existing and newly  
17 captured data, and by actively engaging local MDTs. In its initial stages, this will be done by  
18 demonstrating the variation in the demographics, management and outcomes in the region  
19 using routine NHS datasets. However, given the limitations of what can be achieved with  
20 existing data, the YCR BCIP is collecting additional data to analyse alongside this with the  
21 purpose to better understand what is driving the observed variation.  
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28 The PROMs data will enrich other study data and allow for an 'in-depth' description of what  
29 life is really like for colorectal cancer patients at diagnosis and a year later. At present, the  
30 patient voice is not 'measured' routinely as part of clinical practice, neglecting the impact of  
31 illness and treatment on the everyday lives of patients. YCR BCIP will change this with the  
32 integration of PROMs administration into clinical practice<sup>41</sup>. The PROMs used in this study  
33 have been selected with input from experts in colorectal cancer and psychosocial care:  
34 patients, clinical nurse specialists and doctors. Although the length of the questionnaire  
35 would not be feasible to administer in everyday practice, information on which PROMs  
36 provide the most meaningful data will be obtained. In the future risk-stratified follow-up  
37 may incorporate not only clinical indicators but also key quality of life indicators to inform  
38 best supportive care<sup>44</sup>.  
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48 Results from the tissue collection and testing could impact on treatment and follow-up  
49 decisions for the participating patients and, potentially, their families. For example, the  
50 results may indicate that a patient could benefit from a targeted treatment being tested  
51 through an open clinical trial if they develop an indication for further treatment e.g. Medical  
52 Research Council FOCUS4<sup>45</sup>. Increased risks of having a hereditary condition may be  
53 identified, which not only has implications for the patient but also their family.  
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3 The YCR BCIP is offering a novel approach to address the variation in colorectal cancer care  
4 across a large region of the UK. Engagement of the region's MDTs with their data will lead to  
5 a range of educational initiatives, studies and clinical audits that aim to optimise practice  
6 across the region. It is planned that the outcomes of these will be presented to the relevant  
7 specialty group for review and to develop actions based on findings. The main limiting factor  
8 for the success of the study is that to understand the overall picture of colorectal cancer  
9 care and the ability to improve this in the region, relies on the extent of engagement from  
10 MDTs.  
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### 18 **Ethics and dissemination**

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20 The study was granted ethical approval (17/WM/0374) by the West Midlands – Solihull  
21 Research Ethics Committee in December 2017. The study was approved by the Health  
22 Research Authority and granted approval for inclusion in the National Institute for Health  
23 Research's portfolio of studies in December 2017 (Project ID 227673). Further work from  
24 the seven specialty groups involved in the programme: surgery, radiology, pathology, clinical  
25 oncology, medical oncology, nursing and anaesthetics, will be reported as publications soon.  
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### 35 **Authors' contributions**

36 PQ is the principal investigator. NW, PW and EM are coinvestigators and/or workstream  
37 leads. Together these authors conceived and designed the study. HR and JM manage the  
38 study. JT provides statistical support. AG provides pathology support. All authors  
39 contributed to writing of the manuscript and have approved a final version.  
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### 45 **Competing interests**

46 The authors declare that they have no competing interests.  
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51 Quirke holds an NIHR Senior Investigator award. The UK Colorectal Cancer Intelligence Hub  
52 is supported by Cancer Research UK (C23434/A23706).  
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3 The YCR BCIP study group includes Philip Quirke, Paul Finan, Penny Wright, Nicholas West,  
4 Matthew Seymour, Eva Morris, David Sebag-Montefiore, Daniel Swinson, Damian Tolan,  
5 Simon Howell, Peter Brown, John Taylor, Amy Glover, Aidan Hindley, Hannah Rossington,  
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## Figure Legends

27  
28 Figure 1: Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCRBCIP)  
29 process and study design.  
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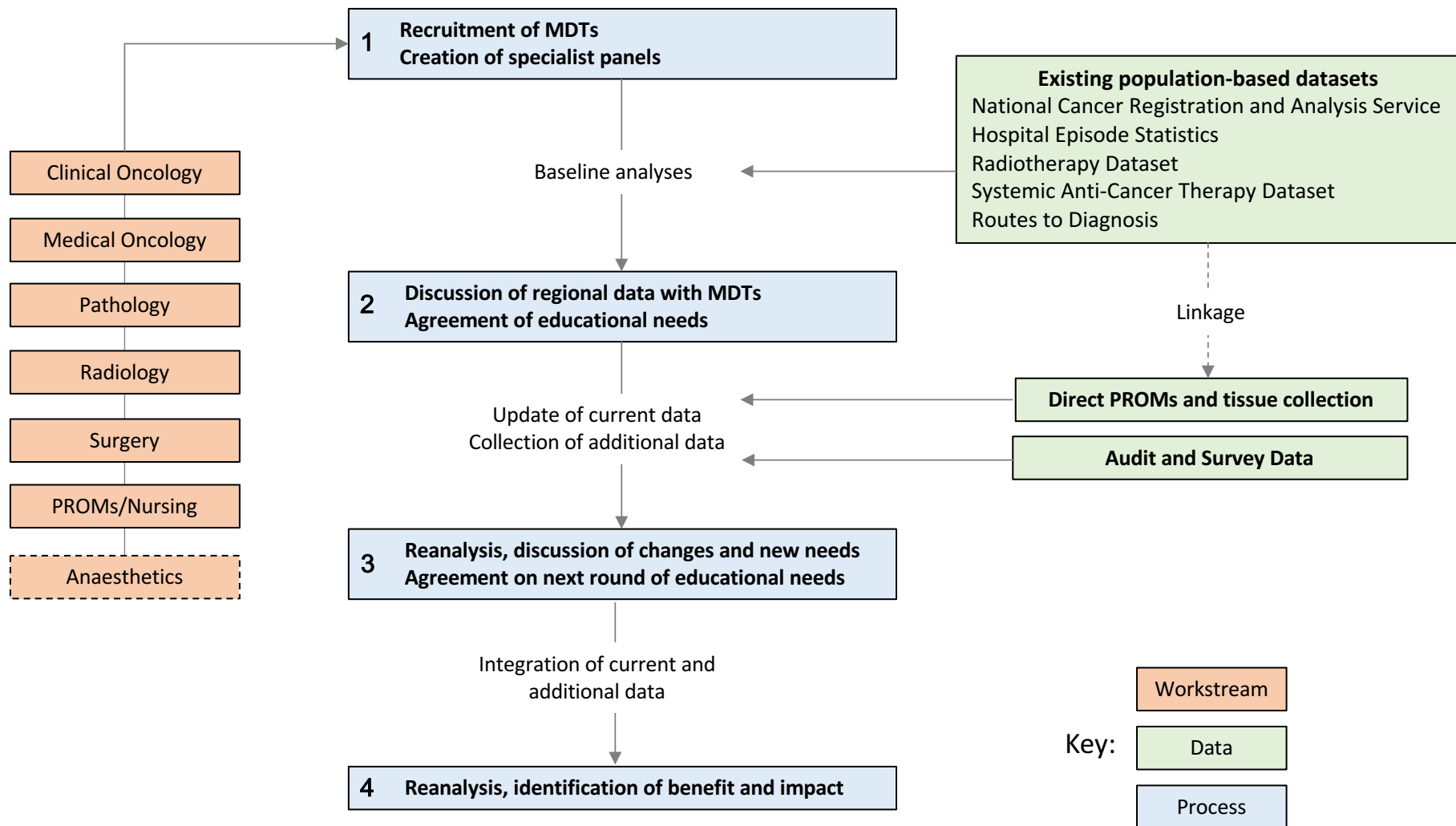
31 Figure 2: Process for the Patient Reported Outcomes Measures (PROMs) study.  
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	Data Source		
	Existing population-based datasets	Direct PROMs and tissue collection	Audit and survey data
<b>Patient and Tumour Characteristics</b>			
Age & sex	NCRAS	PROMs	
Ethnicity	NCRAS	PROMs	
Height & Weight		PROMs	
Comorbidity	NCRAS	PROMs	
Socio-economic status	NCRAS	PROMs	
Stage & site	NCRAS		
Method of admission	NCRAS		
<b>Treatment Variation</b>			
Surgical resection rate	HES		
Quality of surgery			Audit
Abdominoperineal excision rate	HES		
Use of adjuvant & palliative chemotherapy	SACT		Survey
Use of neoadjuvant radiotherapy	RTDS		
Use of laparoscopic surgery	HES		
Emergency care procedures	HES		Survey
Practice of anaesthetics			Survey
Quality of MRI reporting			Audit
Quality of CT imaging			Audit
Liver metastases resection rate	HES		
Nodal yields and retrieval methods	NCRAS		Audit
<b>Outcomes</b>			
30-day Postoperative mortality	NCRAS		
1 to 5 year overall and net survival	NCRAS		
18-month postoperative stoma rate	HES		
Postoperative hospital stay	HES		
Emergency readmission rates	HES		
Overall health and quality of life		PROMs	
Everyday life and well-being		PROMs	
Self-efficacy for Managing Chronic Disease		PROMs	
Financial cost of cancer		PROMs	
Urinary function and faecal incontinence		PROMs	
Sexual functioning		PROMs	
Lower anterior resection syndrome		PROMs	
Molecular subtyping		Tissue	

Abbreviations: Magnetic resonance imaging (MRI), Computerized Tomography (CT), National Cancer Registration and Analysis Service (NCRAS), Routes to Diagnosis (RtD), Hospital Episode Statistics (HES), Systemic Anti-Cancer Therapy Dataset (SACT), Radiotherapy Dataset (RTDS).

**Table 1. Measures of patient characteristics, treatment measures and outcomes to analysed and the corresponding data source.**

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BMJ Open  
Patient Consented

Baseline Online Questionnaire

Baseline Paper Questionnaire

Completed within 2 weeks?

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

Baseline Questionnaire not Completed?

Baseline Questionnaire Completed?

No follow up at 12 months

12 month death check undertaken

Invitation for online or paper questionnaire at 12 months post baseline

Completed within 2 weeks?

Up to 2 reminders sent by study team 2 weeks apart (email or post depending on preference)

12 month Questionnaire not Completed?

12 month Questionnaire Completed?

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