Study Title: A prospective cohort study of Functional and Immunological outcomes after Laparoscopic and Robotic Total Meso-rectal Excision for rectal cancer

FILTER – Functional and ImmunoLogical outcomes of laparoscopic TME and Robotic TME

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Chief Investigator:	**Mr Jim Khan, Consultant laparoscopic and Robotic Surgeon**
Investigators:	**Prof Janis Shute, Professor of Pharmacology, University of Portsmouth** **Mr Filippos Sagias, Consultant Surgeon** **Mr John Conti Consultant Surgeon** **Mr Rauand Duhoky (clinical study coordinator / Trial Manager)** **Mr Sam Stefan clinical fellow** **Ms Karen Flashman (data management)** **Mrs Liz Hawes (Senior Research Nurse)** **Mrs Bethany Armstead (Specialist Research Nurse)** **Mr Pedro Braga Sardo (Specialist Research Nurse)**
Sponsor:	**Portsmouth Hospitals University NHS Trust**
Funder:	**Intuitive Foundation, BASO**
Signatures:	**The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol**

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	FILTER (functional & immunological outcomes after minimally invasive TME surgery, laparoscopic and robotic)
Internal ref. no.	…
Problem statement	Rectal cancers are defined as cancers originating within 15 cm from the anal verge. Since the introduction of the TME surgery (Total Mesorectal Excision) by Heald et al in 1982, the oncological outcome of rectal cancer patients has improved significantly.[1] In recent years surgical techniques (and as a result the TME technique) have evolved from open techniques to several minimally invasive techniques. In TME, the laparoscopic approach is now widely accepted as having similar oncological outcomes as the open technique and having significantly better short-term outcomes, such as a shorter length of hospital admission, smaller wounds, less incidence of postoperative hernias, less intraoperative blood loss and more.[2–5] However, the laparoscopic approach has its own limitations, such as crowding of instruments in the small and narrow pelvis. Other surgical techniques have been introduced in an attempt to overcome these limitations, such as the transanal approach (TaTME) and the robotic approach, though superiority of either of these techniques to the laparoscopic technique has yet to be proven.[6–9] **The stress response** Every surgical intervention causes collateral damage and creates wounds which need to heal. This leads to a stress reaction of the body, which in turn releases cytokines and inflammatory mediators that cause a variety of infectious symptoms known as the SIRS reaction (Systemic Inflammatory Response Syndrome). The severity of the SIRS can be measured with blood analyses. If robotic surgery is more precise than other techniques and leads to less tissue damage during surgery, we hypothesize this could also lead to a reduced inflammatory response postoperatively, which we could measure in postoperative bloods and compare between the laparoscopic and robotic groups. **Functional outcomes** Rectal cancer has always been associated with a high risk of urological and sexual dysfunction due to accidental intraoperative damage to the pelvic nerves. Some have hypothesized that robotic surgery is more precise than other techniques and should lead to less intraoperative damage to nerves and vessels. If this is correct, we should observe better functional outcomes in robotic patients in terms of urological, sexual and bowel function. An earlier study conducted in Portsmouth Hospitals University NHS Trust showed a possible trend towards robotic surgery having better functional outcomes, but this study was done retrospectively and was limited to urological and sexual function.[10] As such, we prepose to expand on this study by conducting this prospective single centre study. Historically most patients who underwent rectal cancer surgery received a (temporary) stoma. With the higher rate of restorative procedures, the bowel function has also become more important, as a better bowel function correlates with a higher Quality of Life. These outcomes can be assessed by using several certified questionnaires

	on various topics (sexual function, urological function, and bowel function) and comparing them between the groups. Robotic technology is relatively expensive to use, but there may be a trend towards improved outcomes in high-risk patients, as seemed to be the case in our previous retrospective study.[10] This could reduce the need for temporary stomas and return to theatre or readmissions, and actually result in overall cost savings compared to other techniques. The aim of this study would be to assess the stress response in postoperative blood samples and the functional outcomes after laparoscopic and robotic rectal cancer surgery in a prospective fashion. Our hypothesis is that robotic surgery causes less of a postoperative stress response with better or similar functional outcomes.
Research question / hypothesis	Does robotic rectal cancer surgery result in a more precise dissection with a reduced immune/stress response and does it lead to better functional outcomes as compared to laparoscopic surgery?
Study Design	Prospective single-centre cohort study
Study Participants	All patients operated for rectal cancer with curative intent using minimally invasive techniques at Queen Alexandra's Hospital in Portsmouth
Planned Sample Size	80
Follow-up duration	12 months
Planned Study Period	December 2021-December 2024
Primary Objective	1. Assessment of sexual, urological and bowel function in patients undergoing rectal cancer surgery 2. Analysing postoperative stress and immune response in blood samples
Secondary Objectives	Assessment of Quality of Life To assess the anorectal physiology after rectal cancer surgery To compare surgical process outcomes between robotic and other types of surgery To compare patient related outcomes relating to recovery between the surgical methods, i.e. length of hospital stay, early morbidity
Primary Endpoint	1. Qualitative functional assessment of sexual, urological and bowel function at baseline and at 3, 6, and 12 months by using: • International Prostatic Symptoms Score (IPSS) (male) • International Index of Erectile Function (IIEF) (male) • Female Sexual Function Index (FSFI) (female) • Kings Health questionnaire (female) • LARS-score (male/female) • Vaizey score (male/female) 2. Measurement of stress response by taking blood samples at baseline and post-operatively on day 1, 3 and 5. The blood will be tested on: • White cell count • CRP • NLR (neutrophil lymphocyte ratio)

	• IL-6 • IL-10 • TNFa • MPO (neutrophil myeloperoxidase)
Secondary Endpoints	QOL assessments by using validated questionnaires at baseline, 6 months and 12 months by using; • QLQ-C30 and QLQ-CR29 • EQ-5D Surgical process outcomes: operative time, blood loss, stoma rate, conversion rate Patient related outcomes: length of hospital stay, opioid requirements and compliance with ERP, worst vital signs post op, worst pain scores, time to flatus (in days) and return of bowel function, early morbidity (up to 30 day postoperative complications, Clavien-Dindo Classification), early mortality, adverse events. Assessing anorectal physiology by using an anorectal manometry at baseline and after 1 year (optional)
Intervention (s)	None

3. ABBREVIATIONS

AE	Adverse Events
AR	Adverse Reactions
ASA	American Society of Anaesthesia
CI	Chief Investigator
CRP	C-reactive Protein
EQ-5D	Euro Quality of life questionnaire
ERP	Early Recovery Program
FESFI	Female Sexual Function Index
IIEF	International Index of Erectile Function
IL-10	Interleukine 10
IL-6	Interleukine 6
IPSS	International Prostatic Symptoms Score
ISRCTN	International Standard Randomised Clinical Trial Number
LARS	Low Anterior Resection Syndrome
MDT	Multi-disciplinary team
MPO	neutrophil myeloperoxidase
NBOCAP	National Bowel Cancer Audit Programme
NHS	National Health Service
NIHR	National Institute for Health Research
NLR	Neutrophil lymphocyte ratio
PI	Principal Investigator
QLQ-CR29	Quality of Life Questionnaire- Colorectal cancer module
QLQ-C30	Quality of Life Questionnaire- Cancer
QOL	Quality of Life
SAE	Serious Adverse Events
SAR	Serious Adverse Reactions
SIRS	Systematic Inflammatory Response Syndrome
TME	Total mesorectal excision
TNFa	Tumor Necrosis Factor alpha

4. BACKGROUND AND RATIONALE

Rectal cancers are common in the western world and make up about one quarter of all the colorectal cancers. Rectal cancers are defined as originating within 15 cm of the anal verge.[11] The primary treatment of these cancers is surgery, either with or without neoadjuvant therapy (chemo- or radiotherapy). As the surgical techniques have evolved over time, outcomes have improved. There was a time when abdominoperineal excision of the rectum was considered gold standard for low rectal cancers, despite leaving everyone with a permanent colostomy and having poor survival rates.[12] Since the introduction of the TME (Total Mesorectal Excision) technique by Heald et al. in 1982, the oncological outcome of rectal cancer patients has improved significantly.[1] During the same time as the introduction of the TME technique, in the late 80's, minimally invasive laparoscopic colorectal surgery made its debut and led to significant improvements in short-term postoperative outcomes.[2,3] This improvement of the surgical technique in combination with the advent of modern instruments has facilitated sphincter saving low and ultra-low anterior resections. Since 1992 the laparoscopic approach has been applied to rectal cancer with promising results.[4,5]

The balance between oncological clearance and function preservation can be achieved with any of the four surgical approaches: open, laparoscopic, trans-anal or robotic. Although laparoscopic surgery has been widely accepted as a better alternative to open surgery in terms of short-term outcomes, its adoption in general practice for rectal cancers in the UK remains low. According to NBOCAP, 28% of the colorectal cancer patients in the UK are still treated with open surgery.[13] The laparoscopic approach is based on a long learning curve and many of it's critics cite the high conversion rates, lack of flexibility of the instruments and limited hand-eye coordination with lack of tactile perception.[6,7] In order to overcome these limitations other minimally invasive techniques, such as robotic surgery and the trans-anal approach (TaTME), were introduced as an alternative to laparoscopic surgery.[8]

The current focus is not only on the complete clearance of neoplastic lesion, but also on preservation of the function. This is even more challenging for mid to (very) low rectal cancers, due the combination of a narrow pelvis, difficult access, and proximity of other structures. The Da Vinci robotic system was introduced to achieve an optimal functional outcome after anterior resection. The advantage Da Vinci has over the conventional laparoscopy is seven degrees of instrument movement, a fixed camera to provide stable operative view and the ability to filter out tremors. It is also less exhausting for the surgeon, who can take regular breaks to improve the surgical efficiency and perform the procedure more comfortably. The availability of robotic surgery as an option for patients is limited by the upfront expense that comes with the purchase of the systems and the subsequent maintenance costs. Additionally, there is a limited number of surgeons trained to perform complex procedures with these systems, and adequate training takes time for both the trainees and those with sufficient expertise to train others.

The debate whether robotic assisted surgery is superior to laparoscopic surgery is still ongoing.[9] The lack of significant differences between them could be due to surgical trials being performed with robotic surgeons still in the beginning of their learning curve. In addition to this, a lot of robotic research is being done in Asian countries, which have a different population with less obesity[14–18]. Because of this, the advantages of the robotic approach may be dampened as compared to operations in Western, more obese populations, which means there is still a need for ongoing research comparing the different minimally invasive techniques (in Western populations).

Every surgical intervention creates a wound, which leads to a stress response of the body with the release of cytokines and inflammatory mediators. These can cause a variety of symptoms commonly referred to as SIRS (systemic inflammatory response syndrome), which can be measured with blood analyses. The magnitude of this SIRS response is directly related to the risk of post-operative complications, such as ileus, pain and opioid requirements. It is postulated that the degree of SIRS response decreases in a stepwise fashion when the choice of approach in rectal cancer surgery moves from open to minimally invasive (laparoscopic, trans-anal and robotic).

The ability to perform a more precise dissection in robotic surgery could result in minimal tissue damage and hence reduced SIRS. With every surgery there is also a risk of accidentally damaging structures, such as vessels and nerves. Rectal cancer surgery has always been associated with a high risk of harming such structures, due to the complexity of the surgery and the small surgical field[19–21]. Damaging the pelvic nerves can lead to severe urological, sexual and/or bowel function disorders. More and more surgeries are being performed in a restorative setup, which means the bowel function is becoming increasingly important. Studies have shown that the functional outcomes in rectal cancer patients is related to their Quality of Life outcomes[19,20,22–24]. These functional outcomes can be assessed through several certified questionnaires on each topic (sexual function, urological function, and bowel function) and compare the outcomes. An earlier study in our hospital suggested a possible trend towards robotic surgery having better urological and sexual functional outcomes.[10]

Although robotic technology is expensive to use, there may be a trend towards improved outcomes in high-risk patients. A long-term improvement of functional outcomes would reduce overall costs in the long run. There's also the possibility of shorter length of hospital stay with the robot-assisted procedures, which could also save money.[25] Moreover, with a more precise operative technique, surgeons are less likely to use preventive temporary ileostomies. Across the UK there is a wide variation in the proportion of patients that receive a permanent stoma at surgery (7% - 83%), and around 30% of patients will have an unclosed ileostomy at 18

months.[13] Less temporary ileostomies would significantly cut costs through fewer stoma reversal surgery, less hospital admittance, no stoma bag training and no stoma bag materials. If a small group of patients do develop a Low Anterior Rectum Syndrome, they can still receive a stoma later.

The aim of this study is to assess the post-operative stress response measured in blood in combination with functional outcomes after laparoscopic and robotic rectal cancer surgery. The study will be set up in a prospective fashion with the hypothesis that robotic surgery causes less of a stress response, along with better or similar functional outcomes.

5. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

The literature available on the surgical stress and immunological response following surgery, and specifically rectal cancer surgery, investigate different immune markers and comparing different types of surgery, leading to mixed results. In addition to this, the studied cohorts are often too small to draw a significant conclusion from the results.

Functional outcomes

In a recent meta-analysis by Ohtani et al. the functional outcomes after rectal cancer surgery between robotic and laparoscopic surgery were compared and their sub-analysis included data from 9 articles. As depicted in the table below, the largest studies came from Asian countries. Their conclusion is that both urological and sexual dysfunction did not differ significantly between the two groups, with a Urological Odds Ratio of 0.85 (95%CI 0.57-1.26, p=0.41) and Sexual Odds Ratio of 0.54 (95%CI 0.19-1.58, p=0.26)). Most of the articles only report a short-term complication rate (<30 days) for urinary retention. These have a range of different causes, for example urinary catheter use, epidural analgesia or inflammation/swelling of the tissues. A long-term validated assessment tool, such as the IPSS questionnaire for urological function and the IIEF for sexual function, would be more insightful for the outcomes. The 3 studies that do use these methods for urological function assessment (Cho, Kim N.K. and D'Annibale) show a favourable or similar outcome for the robotic technique. The 5 studies using IIEF for sexual dysfunction show a trend towards better results for the robot, (see table 1). Two studies also mention faecal incontinence to be less severe with the use of the robot but provide no information on the methods used to assess this.[9,14–17,26–31]

Table 1: Overview functional outcome articles, Ohtani meta-analysis[9,14–17,26–31]

Article	Year	Country	Patients R= Robotic L= Laparoscopic	Urinary retention/ complication (<30 days)	IPSS/ urodynamic study (>30 days)	Sexual dysfunction /IIEF	Fecal incontinence
Alleman	2012-2014	Swiss	R 20 L 40	1 2	-	-	-
Cho	2007-2011	Korea	R 278 L 278	5 (1,8%) 11 (4.0%)	2 (0.7%) **12 (4.3%)**	7 (2.5%) 6 (2.2%)	6 (2.2%) 3 (1.1%)
Fernandez	2002-2012	USA	R 13 L 59	18 (53%) 5 (39%)	-	-	-
Silvia-Velazco	2010-2014	USA	R 66 L 118	10 (15.2%) 15 (12.7%)	-	-	-
Patriti	2004-2008	Italy	R 29 L 37	1 (3.4%) 1 (2.7%)	-	1 (5.5%) 3 (16.6%)	2 (6.8%) 1 (2.7%)
Park	2007-2009	Korea	R 52 L 123	0 2 (1.6%)	-	-	-
Morelli	2009-2014	Italy	R 50 L 25	4 (8%) 1 (4%)	-	-	-
Kim NK	2008-2009	Korea	R 100/30 L 100/39	4 (4%) 9 (9%)	N > 3 mo -	N > 6 mo -	-
Kim JC	2010-2015	Korea	R 533 L 486	29 (5%) 29 (6%)	-	19.1% 25.6%	-
D'Annibale	2006-2012	Italy	R 30 L 30	-	N > 1 y N > 1 y	N > 1 y +/- N > 1 y	-

Stress-response

Evidence on the stress response after surgery is lacking. There are a few studies on the subject, but almost none on colorectal surgery, and no systematic reviews or meta-analyses. The studies that do report colorectal surgery are summarised in table 2. The studied variables are very heterogeneous, groups are small and almost all compare open surgery with a minimally invasive technique (either robotic or laparoscopic), finding a statistically significant difference.[18,32–34]

There has only been one study that compared laparoscopic colorectal surgery with robotic colorectal surgery for stress response, which is Shibata et al.[18] They compared the surgical stress response after open, laparoscopic and robotic colorectal surgery. As expected, the open group showed the highest magnitude of surgical trauma after surgery. The robotic HLA-DR had a statistically significant difference with the open group on day 3, but not with laparoscopic. CRP was slightly lower on day 6 for the robotic patients compared with laparoscopic, but wasn't statistically significant. A possible explanation for the comparable outcomes between the laparoscopic and robotic groups is that all the tumours in the robotic group were in the rectum. This is assumed to cause more surgical stress than a colon resection, which is also mentioned in the discussion of the study.

Table 2: Overview articles on stress response[18,32–34]

Article	Year	Country	Approach	Surgery	Markers	Time points	Conclusion
Shibata	2012-2013	Japan	Colorectal Open (8) Lap (23) Robot (15)	Left hemi LAR, high-AR, ISR, sigmoid	HLA-DR, CRP, Lymphocyte subset	Pre-op Day 1 Day 3 Day 6	HLA-DR: RS>OS, RS=LS CRP: OS > LS/RS, Day 1 LS<RS day 3 max OS/LS/RB, day 6 RS<LS (non-sig)
Krzystek-Korpacka	2013-2015	Poland	Colorectal Open (31) Robot (30)	?	IL7, Lymphocyte count, Lymphocyte/ neutrophil ratio	Pre-op 8 hr 24 hr 72 hr	Lymphocyte count drop R<O IL-7: R steady increase, O Rise and drop Pre-op IL7 levels are linked with lymphocyte decline and neutrophil-lymphocyte ratio
Zawadzki	2013-2015	Poland	Colorectal Open (28) Robot (33)	Left colon, right colon, **rectum**	IL-1B, Il-1, IL-6, TNFa, CRP, procalcitonin	Pre 8h Day 1 Day 3	IL-6: R<O after 8h TNFa: CRP: R<O after 24h (sig) Rctl PCT: R<O 8h/24h/72h (Sig)
Veenhof	2006-2008	Netherlands	Rectal Open (18) Lap (22)	**Rectal**	White blood cell count, monocyte count, CRP, IL-6, IL-8, HLA-DR, growth hormone, cortisol	Pre-op 2 hr 24 hr 72 hr	HLA-DR: L>O 2h (sig) IL-6: L<O 2h (sig) Other markers no significant difference

Our own experience

In a previously published article about the outcomes of robotic surgery versus laparoscopic surgery in high-risk patients in Portsmouth hospital the robotic group showed a significantly higher sphincter preservation rate, shorter operative time, shorter hospital stay (7 vs 9 days), less blood loss and a lower conversion rate to open surgery.[35] The male gender, obesity (BMI>30), pre-operative chemo-radiotherapy, low rectal tumours and history of abdominal surgery are the most important risk factors for these patients, and can make any surgical approach more challenging. Furthermore, in a retrospective study by Panteleimonitis et al. patients were asked to fill in questionnaires on their urological and sexual function after laparoscopic (n=78) and robotic surgery (n=48) for rectal cancer.[10] This study did not, however, assess bowel function for their population. It showed a better function outcome for the robotic group, but due to its retrospective nature there is a risk of recall bias with patients not being able to accurately recall their pre-operative function.

In summary, there is some evidence regarding functional outcomes and stress response after colorectal surgery, but the studies are very heterogeneous and the results are not directly transferrable to our specific rectal cancer patients group. There is also no evidence available linking the stress response with the functional outcomes. This observational cohort study would fill in these gaps in the current literature and could function as evidence for further research.

Lay Summary

THE PROBLEM

Cancer of the rectum, which is cancer in the last 15 cm of the large bowel, is a common type of cancer. The treatment for this type of cancer is taking out the whole tumour with an operation. This used to always be done with an open procedure, leaving a big scar, and is still the case for 28% of rectal cancer patients in the UK. With the rise of key-hole surgery we can do the same surgery with smaller wounds, leading to a shorter recovery time after surgery, but the standard (laparoscopic) key-hole surgery has its own limitations. An example of this is that it is hard to navigate deep in the pelvis with the current 'laparoscopic' key-hole instruments, which can lead to accidentally harming structures such as blood vessels or nerves. Harming these structures can lead to sexual dysfunction and problems with urinating or bowel control. To try and limit these unwanted side-effects other new techniques have been introduced, one of which is the robotic technique.

This robot (called 'Da Vinci') is a more flexible device with a wider range of controlled movements, is equipped with a 3D camera (leading to better vision) and allows for a more precise removal of the tumour. We think this technique will cause less harm to the surrounding structures, leading to a better outcome of the urological, sexual and bowel function.

A way to measure the harm that is done by a surgery is by measuring the stress response in blood. Every surgery causes wounds that the body needs to heal. This healing process is more severe when larger wounds are made and can be measured in the blood. We believe that with robotic surgery the size of the surgical wounds can be reduced and cause a less severe surgical stress response.

THE STUDY

This study is looking to recruit a group of 80 patients with rectal cancer who are referred to the surgical department at Queen Alexandra Hospital for a surgical resection. We will compare the standard laparoscopic operation (Total Mesorectal Excision (TME) surgery) with robotic TME surgery. To compare the surgical stress response, we will take blood samples before the surgery and on day 1, 3 and 5 after the surgery. If all goes well day 5 is usually the day a patient is discharged home after this kind of surgery. To compare the functional outcomes, we will ask the patients to complete several questionnaires on urological function, sexual function, bowel function and general quality of life at several moments: before the surgery and after 3, 6 and 12 months. The research team will also gather further information about the recovery and cancer treatment by reviewing the patient's hospital notes for 1 year. This study will not affect the surgical after care of patients in both groups. After completing this study, we will

have better insight into which operation is better at causing the least harm to the surrounding structures when removing a rectal tumour.

6. AIMS AND OBJECTIVES

6.1 Main Hypothesis

Robotic surgery for rectal cancer results in a milder stress response and similar or better functional outcomes when compared to the laparoscopic approach.

6.2 Primary Objectives

1. Assessment of sexual, urological and bowel function in patients undergoing rectal cancer surgery
2. Analysing postoperative stress and immune response in blood samples

6.3 Secondary Objectives

1. Assessment of Quality of Life
2. Assessment of the anorectal physiology after rectal cancer surgery
3. To compare surgical process outcomes between robotic and laparoscopic rectal surgery
4. To compare patient related outcomes relating to recovery between the surgical methods, such as length of hospital stay, early morbidity and others

7. STUDY DESIGN

7.1 Summary of Study Design

A prospective, single centre, observational study with qualitative assessment of sexual, urological, bowel function and stress response in patients with rectal cancer comparing robotic surgery with laparoscopic surgery.

7.2 Primary and Secondary Endpoints/Outcome Measures

Primary endpoints:

1. Assessment of functional outcomes by using validated questionnaires for bladder, bowel and sexual function pre-operatively, and after 3, 6 and 12 months.
    - International Prostatic Symptoms Score (IPSS) (male)
    - International Index of Erectile Function (IIEF) (male)
    - Female Sexual Function Index (FSFI) (female)
    - Kings Health questionnaire (female)
    - LARS-score (male/female) – Not applicable at 3 and/or 6 months if the patient still has a stoma in situ at those respective follow-up moments
    - Vaizey score (male/female)
2. Measurement of stress response by taking blood samples at baseline and post-operative days 1, 3 and 5. Blood samples can be collected by anyone trained to do so and will be processed by an appropriately delegated member of the clinical team (including the research team). The following blood tests will be collected:

- White blood cell count (WBC)
- C-reactive protein (CRP)
- NLR (neutrophil lymphocyte ratio)
- IL-6
- IL-10
- TNFa
- MPO (neutrophil myeloperoxidase)

Some of the above blood tests (WBC, CRP, NLR, etc.) may be carried out as part of routine post-operative care. If these results are available, they can be used and additional sampling may not be required. Should these test results also be available for postoperative days 2 and 4, they can also be collected for use in this study, but this will be optional and no additional sampling will be done on these days.

Secondary outcomes:

1. Quality of life assessment using validated questionnaires (EORTC QLQ-C30/ CR29 and EQ-5D) at baseline, and after 3, 6 and 12 months.
2. Surgical outcomes, such as operative time, blood loss, stoma application, conversion, and intra-operative complications
3. Patient related outcomes:
    a. Length of hospital stay
    b. Opioid requirements and compliance with ERP
    c. Worst vital signs post op
    d. Worst pain scores
    e. Time to flatus (in days) and return of bowel function
    f. Early morbidity (up to 30-day postoperative complications, Clavien-Dindo Classification*)
    g. Early mortality
    h. Adverse events.
4. Optional: assessment of anorectal physiology after laparoscopic or robotic surgery in rectal cancer patients by using an anorectal manometry at baseline and after 1 year
    a. Assessment will be done in the outpatient clinic when patients come for their standard care preoperative and 12-month follow-up visit. The manometry will be performed by the clinical team using departmental equipment.

*Clavien-Dindo classifications.[36]

Grade I - Any deviation from normal post-operative course without the need of pharmacological or surgical intervention
Grade II - Requires pharmacological treatment
Grade III - Requires surgical, endoscopic or radiological intervention
Grade IV - Life threatening complication/ requiring ICU management
Grade V - Death of a patient

8. STUDY PARTICIPANTS

8.1 Study Setting

80 patients with rectal cancer with an elective indication for surgery will be recruited from Queen Alexandra Hospital in Portsmouth during an estimated 2-year period. This study will be observational, and all data will be collected prospectively.

The reason for choosing an observational study is that there is very little evidence on the subject. To run a randomised controlled trial at this moment, without evidence that there might be a trend towards a significant difference, would be a very costly decision with a possibly unjustified burden to the patients.

Since the unit performs over 100 rectal resections a year amongst 3 surgeons and there is an approximately equal split between robotic and laparoscopic cases, randomisation for creating equal groups will not be necessary in this stage.

If this observational study proves to be of significant value, we will proceed with a larger, multi-centre randomised trial, taking these results into account in the designing stages.

8.2 Overall Description of Study Participants

Patients with rectal cancer, up to 15 cm from the anal verge, with an indication for elective minimally invasive rectal cancer surgery.

8.3 Eligibility Criteria

Patient Inclusion Criteria

- Age 18 years or above.
- Diagnosed with rectal cancer, up to 15cm from the anal verge.
- Local MDT recommends rectal cancer surgery (i.e. (high) anterior resection, partial TME, complete TME)
- Patient assessed as fit for surgery (ASA I-III).
- Patient willing and able to give informed consent for participation in the study.
- Elective surgery.

Patient Exclusion Criteria

- Patient planned for Abdominoperineal Excision of Rectum (APER) or Hartmann's procedure
- Patients with confirmed or suspected metastatic disease.
- Pregnant or breastfeeding patients.
- Inflammatory bowel disease (IBD).
- Other known auto-immune disease which might influence the immune response (such as advanced liver disease, human immunodeficiency virus infection, Hepatitis B or C virus).
- Use of anti-inflammatory medication (i.e. corticosteroids, anti-inflammatory drugs, immune modulating drugs, chronic use of antibiotics (the use of NSAIDS and steroid asthma inhalers will not be considered an exclusion criteria).
- High pre-operative C-reactive protein (CRP) levels (>20).

9. SAMPLING

In our retrospective study we demonstrated IPSS and IIEF score differences of more than 5.0 points between the 2 groups (see preliminary data). Assuming a 3.75 IPSS score and 4.4 IIEF score difference and a 0.05 (two-sided) significance level, 35 patients will be required in each group to provide 80% power.

We also carried out simulated cumulative scores from the study-specific CRF based on the Likert-scale for independent validation of our initial analysis. Considering 80% power and a 0.05 (two-sided) significance level, a minimum of 36 patients were needed in each arm to demonstrate a minimum difference in the cumulative score of 1 between the groups. This sample size calculation was carried out using the “stats” module in R (ver. 3.4.2) using a two-sided independent means test.

We have considered a maximum of 10% loss to follow-up for the long-term functional outcomes in our population during sample size calculations and will thus seek to recruit a minimum of 80 patients into our study.

10. STUDY PROCEDURES

10.1 Recruitment and informed consent

The study will be offered prospectively to patients undergoing elective bowel resection for colorectal cancer or benign pathological cancer. Following the decision to operate, the clinical team will identify these patients as potential patients and introduce them to the study. The Participant Information Sheet (paper or digital) will be given to potential patients in person or remotely (via post or email).

Patients will be given sufficient time to consider their involvement and ask any questions they have. Potential patients will be clearly informed that involvement is completely voluntary, and they can decline or withdraw at any time without reason or penalty. We will retain the data we have already collected if they withdraw and will continue to collect information from their medical records unless they ask us not to.

The Prime Investigator has overall responsibility for informed consent at their site to ensure staff listed on the delegation log are appropriately trained, experienced and competent in receiving informed consent. Informed consent will be received by an appropriately trained member of the research team who has been delegated to do so and has been signed onto the delegation log for this task by the CI/PI.

In person informed consent

Patients will be provided with the study information as described above. Patients are able give informed consent once they feel they have had sufficient time to consider participation. No minimum timeframe is defined, as some patients may read the information and wish to consent at that time. After consent, patients will have the opportunity to further consider their involvement and withdraw by contacting the research team. Patients who wish to have more time to consent are able to do so and, when ready, can give informed consent remotely to prevent additional visit burden.

Remote consent

Remote consent can be received by witnessed verbal consent via telephone or by trust approved video call platforms. Patients will be provided (in person/ post / email) with a copy of the Participant Information Sheet (paper or digital) to read and review. The call/video must be witnessed by a member of staff at site who is not part of the study team (this may be a member of the clinical team or a research nurse from another team) who will confirm in writing that the study was explained, questions were answered, time was given for patients to consider and patients were informed that all involvement is voluntary and that they can withdraw at any time without penalty (this document should be signed and a copy filed in site file and patients medical notes). After remote verbal consent is received the member of the study team receiving consent will sign the consent form and clearly document the consent was performed via remote witnessed consent. The consent form is to be countersigned by the witness. The original consent form should be filed in the site file, a copy of the consent form provided to the patient (post or email) and another copy filed in the medical notes. There will be no active recruitment strategy (such as advertisements) other than selecting patients from the participating centres by the research team, see below.

Recruitment time frame

The unit performs over 100 rectal resections a year with 3 surgeons and there is approximately an equal split between robotic and laparoscopic cases. Therefore, we estimate 100 potentially eligible cases will take place each year. Allowing for exclusion criteria and patients declining participation, and assuming a recruitment rate of 60%, we estimate recruitment will be completed two years from study opening.

10.2 Study Assessments

Procedure	Baseline assessment (-31 days to "Day of surgery")	Pre-operative blood samples (-96 hours to "Day of surgery")	Day of surgery	Postoperative days 1, 3 and 5	30 days (can be completed retrospectively)	3 months (+- 2 weeks) and 6 months (+- 6 weeks)	12 months (+- 6 weeks)
Check eligibility criteria (by a delegated member of the research team)	X						
Informed consent	X	X	X				
Start CRF, record in notes, inform GP	X						
Anorectal manometry (optional)	X						X
QOL and functional questionnaires	X					X	X
Blood samples		X		X			
Patient records (including adverse events)					*X*	*X*	*X*

Baseline assessments

The baseline information will be collected on the CRF (case report form) following informed consent. They will be completed by the research nurse or appropriate GCP licensed member of the surgical team. Data will include:

(i) Socio-demographic variables: age (years), gender

(ii) Physical examination: weight, height, BMI

(iii) Medical history: ASA (American Society of Anaesthesiologists physical classification), previous abdominal surgery, other co-morbidities

(iv) Radiological findings/conclusion MDT: TNM classification, mean distance from anal verge (cm)

(v) Anorectal manometry measurement (optional)

(vi) Patient-reported outcome measures (PROMS):

Validated QOL questionnaires: EORTC-QLQ-C30 (cancer patients), C29 (colorectal cancer specific) and EQ-5D.

Validated functional outcome questionnaires on bowel, urological and sexual function: LARS, Vaizey score, IPSS (males), IIEF (males), FSFI (females), Kings Health (KHQ) questionnaires, see below.

(vii) Baseline and post-operative blood samples (taken within 4 days before surgery):

- White cell count (WCC)
- CRP
- Neutrophil lymphocyte ratio (NLR)
- IL-10
- IL-6
- TNFa
- MPO (neutrophil myeloperoxidase)

Questionnaire surveys will include:

- **European Quality of Life-5 Dimensions (EQ-5D**) – this is one of the most well-known and commonly used generic measure of health status internationally, available in 169 languages and recommended by the National Institute for Health and Care Excellence (NICE) for use in its health technology appraisal process.
- European Organization for Research and Treatment of **Cancer Quality of Life Questionnaire, EORTC QLQ-C30 and CR29** (version 3). These are cancer-specific and colorectal cancer-specific respectively, quality of life questionnaires that have been internationally validated and frequently used in the current literature.
- **Low Anterior Resection Syndrome, LARS** – this is a simple 5-question tool established in Denmark in 2012 and validated in English in 2014. This internationally validated score attempts to specifically assess function in patients undergoing low anterior resection surgery. If patients still have a stoma in situ at 3 and/or 6 months, this questionnaire will be skipped for those timepoints.
- St Marks Faecal Incontinence tool, **Vaizey score** – this questionnaire was created in 1998 at St Marks hospital in the UK and allows comparison with historical data that also used the similar Wexner score and other center's published results.
- **International Prostate Symptom Score, IPSS** – this is a simple 8-question tool that has been validated internationally and adopted as the global standard for urological

symptom scoring. **Kings Health questionnaire, KHQ,** is a 21-item questionnaire to evaluate the impact of urinary incontinence on the quality of life in women.

- Sexual function questionnaires: including **International Index of Erectile Function, IIEF, for males** – this is a 15-question validated questionnaire which is the most widely used to assess erectile dysfunction and considered as 'gold standard' by global health entities. The **Female Sexual Functional Index (FSFI)** evaluates, as the name says, the sexual function in women in 19 questions.

Questionnaire completion

If patients are included in multiple studies using one or more of the same questionnaires as described above, the research team is allowed to use these answers for this study as well, rather than burdening the patient with extra unnecessary paperwork. The criteria for this are:

- The version of the forms used for the other study is the same as the version described in this study;
- The questionnaire was completed within the appropriate timeframe as described above;
- An appropriately delegated member of the research team is responsible for trans scripting the filled in form for use in this study.

If patients are for any reason unable to complete one or more of the questionnaires, these will be noted as "unknown", and the patient will remain included in the survey. Patients will have the option for retrospective completion of the baseline questionnaires with a maximum of 30 days after the previously described timeframes.

Delays in surgery

If surgery is delayed, patients will be given the opportunity to remain in the study and consent will be reaffirmed once they have a new surgery date. If the delay is greater than 6 weeks, baseline analyses will be repeated.

Post-operative hospital admission to discharge

Patients will receive standard post-operative care as per clinical pathways, with all treatment decisions made as per clinician expertise. Study blood samples will be collected on days 1, 3 and 5. Routinely patients are expected to be discharged on day 5, but if a patient is discharged home earlier than this there will be no need for additional blood sampling after discharged. For the purpose of calibration, we may need to draw extra blood for the first 10 patients. All study bloods are to be processed as per lab manual and routine blood tests (WBC, CRP, NRL, etc.) will be processed as per local procedure.

Follow-up visits

<u>30 days</u>
Around 30 days postoperatively, the patient's records will be checked to assess postoperative complications, readmissions, patient related outcomes, surgical outcomes, and adverse events.

<u>3 months</u>
At months postoperatively, the patient will receive the questionnaire surveys to fill out (digitally or by mail) and will be contacted by the research team (digitally or by phone) for follow-up and to answer any questions regarding the study.

<u>6 months</u>
At 6 months postoperatively, the patient will receive the questionnaire surveys to fill out (digitally or by mail) and will be contacted by the research team (digitally or by phone) for follow-up and to answer any questions regarding the study.

<u>12 months</u>
At 12 months postoperatively, the patient will attend a standard care follow-up visit with the

clinical team, who will perform an anorectal manometry if possible. They will receive the questionnaire surveys to fill out (digitally, by mail or in person) and will be contacted by the research team (digitally, by phone or in person) for follow-up and to answer any questions regarding the study.

The study does not require any additional investigation or patient contact throughout its duration.

10.3 Discontinuation/Withdrawal of Patients from Study Treatment

Patients can withdraw at any point in the study without penalty. If patients withdraw any data already collected will be used and we will continue to collect outcomes from patient's medical, hospital and NHS notes, unless the patient asks us not to do so.

10.4 Definition of End of Study

The end of study will be the date of the last questionnaire assessment of the last patient.

11. ASSESSMENT OF SAFETY

11.1 Definitions

The safety of robotic and laparoscopic rectal surgery has already been established.[37–39] Robotic and laparoscopic rectal surgery is routinely practised in the participating unit. Patients are offered either surgical modality depending on surgeon and theatre availability. This study does not introduce any new therapies or treatments and does not alter post-operative care or follow up in any way. Therefore, patients are not exposed to any additional risks or complications as a result of this study. Any complications or adverse events following surgery will be highlighted and dealt with according to each unit's standard practice. Since this study does not affect the patient's normal care in any way the normal care pathways will not be altered. Therefore, there are no adverse reactions or serious adverse reactions associated with this study. Since adverse events will be dealt with according to the normal care pathways they do not need to be reported to the sponsor or the principal investigator.

Serious adverse events (SAE) are defined as adverse events that results in patient hospitalisation, a life-threatening situation or death. SAEs need to be reported in order to prevent inappropriately contacting the patient or their family to attend follow up appointments. SAEs will be identified by the research team of each unit and reported to the principal investigator.

11.2 Reporting Procedures for Serious Adverse Events

Only SAE's deemed by the PI to be directly caused by this study will be reported as SAE's. SAE's will be reported as per GCP guidelines.

11.3 Recording and Reporting Procedures for All Adverse Events

Only adverse events that are deemed by the PI to be directly caused by this study will be collected as per GCP guidelines. Venepuncture will be conducted as part of this study, and it will be conducted as per local policy. It will be done by appropriately trained and experienced staff, and will be of no greater risk than in routine clinical care.

Other adverse events will be dealt by the local hospital according to the local care pathways and do not require reporting.

11.4 Recording and Reporting Procedures for Complications or Death

Serious complications (leading to hospitalisation or death) need to be reported by the local research team to the principal investigator. This will be done by email or telephone and is done to ensure that the patient or their family are not inappropriately contacted to attend the follow up clinic.

12. DATA HANDLING AND RECORD KEEPING

12.1 Data Collection Forms

Eligibility criteria for screening will be recorded on the screening log and if a patient is recruited, the data will initially be collected in an eCRF stored in a secure database.

Data will be collected on printed forms or digital forms and uploaded to a secure electronic database. To improve return rate of the questionnaires, patients will have the option to fill them in through a secure online survey program.

Source data/documents (such as patient notes) are kept within the participating hospital medical records department and can be accessed as required through the standard request mechanism for audit. (e)CRF's will be stored for 15 years after the study has been completed.

12.2 Data Management

All identifiable information will be held in a secure database in line with the NHS digital policy. Patient data will be pseudonymised by allocation to an individual study number. Data will be stored in a password encrypted electronic database on an NHS computer. Only the members of the direct clinical and research team will have access to patient identifiable data. Data pro-formas will be stored along with the consent forms and other project documents in a master file and locked in a secure office. The research fellow(s) (or appointed research nurse) will be responsible for data collection, recording and quality.

This study is compliant with the principles of the General Data Protection Regulation (GDPR, 2016) requirements.

13. DATA ANALYSIS

13.1 Description of Analysis of Populations

Subjects from each cohort will be analysed separately. The populations will be defined as per protocol analysis, e.g., patients who completed the treatment as was originally allocated will be included in the analysis, as well as eligible subjects with no minor or major protocol deviations. Descriptive statistics will be provided for all discrete variables in the form of rates and proportions with 95% confidence intervals. Continuous variables will be described by mean, standard deviation, median and range.

13.2 Analysis of Endpoints

We will analyse summary statistics for each allocation group, including means and standard deviations for normally distributed data and medians and interquartile ranges for non-normally distributed data.
Student's t test will be used to analyse the differences between the two groups (L-TME vs. R-TME). The paired t test will be used to compare postoperative urogenital, bowel and sexual functions in both groups to the preoperative functions. Fisher's exact test will be used for categorical data (e.g., age, sex, tumour location, T and N stage, and radiation therapy). A P-value of 0.05 will be considered statistically significant.
The analysis of the differences between groups of blood cell counts or number of lymphocyte subsets, and clinic pathological variables will be performed using Chi-square tests, Kruskal–Wallis tests, and analysis of variance tests. A P-value of 0.05 will be considered statistically significant.

Analysis of the QLQ-C30 and QLQ-CR29 questionnaires will be performed in accordance with the EORTC guidelines. Time to definitive deterioration in quality of life, with the use of a 10-point minimal clinically important difference, will be analyzed with the use of the Kaplan–Meier method and the log-rank test. Descriptions (by visit) and graphs will be presented.

13.3 Procedure for Dealing with Missing, Unused and Spurious Data

There will be no imputation of missing values.

13.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Minor alterations can be made by agreement with PI and must be documented accordingly.

13.5 Interim analysis and criteria for early study termination

The trial management group (TMG) will meet as defined in the study Grant chart. The TMG must concur that all training and study logistics are in place prior to opening to recruitment. At six months after opening, an independent blinded interim analysis will be presented to the TMG and study advisory. Should any of the following futility criteria be met, the study will close:

- Insufficient recruitment (defined as <50% of expected)

14. ETHICS

[Insert ethical approval information when received].

14.1 Participant Confidentiality

The study staff will ensure that the patients' anonymity is maintained. The patients will be identified only by initials and an ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.2 Declaration of Helsinki

The study protocol will be carried out in accordance with the declaration of Helsinki.

14.3 ICH Guidelines for Good Clinical Practice

All investigators and research staff working on the study will have a current Good Clinical Practice training certificate.

15. PATIENT PUBLIC INVOLVEMENT (PPI)

This project has been discussed with our patients and members of the public throughout all stages of its design. The project has been well received by our local Bowel Cancer Support Group, with constructive feedback that has shaped this proposal.

Past patient involvement has particularly aided the design of the patient information leaflet, lay summary and after suggesting if there was a possibility to return the different questionnaires online, this was implemented in the study-design.

A member of the PPI group will sit on the Trial Management Group and will be involved in overseeing the conduct of the study. A lay summary of this study will be included on the Cancer Research UKwebsite.

16. FINANCING AND INSURANCE

16.1 Research Costs

Research costs have been calculated by the Sponsor's finance officer. The funding received covers the costs of study delivery. Any variation in costing between the estimates and the received funding will be covered by the trust.

Total costs for this study will be £65,799.04.

See supplement for a breakdown of the costs.

16.2 Study Sponsorship

Portsmouth Hospitals University NHS Trust will sponsor this study.

17. TIMETABLE AND ORGANIZATIONAL CHART

- Approvals	Month 1 (11/2021)
- Piloting of data collection tool and subsequent review	Month 2 (12/2021)
- Data collection period – first inclusions	Month 3 (01/2022)
- Data collection period – last inclusions	Year 2, Month 3
- Data collection period – last follow-up visits	Year 3, Month 3
- Data summaries	Bi-annually
- Presentation/publication of preliminary results	Year 3
- Writing up reports / publications / dissemination onwards	Year 3, Month 3

18. RESOURCES AND PHYSICAL FACILITIES

The study will be conducted on NHS Queen Alexandra Portsmouth Hospital inpatients admitted in the course of their routine work-up and surgery, and follow-up in the same hospital.

The equipment required is already in the Trust and include:

- Laparoscopic stack, ports, instruments, sutures & dressings required to perform the procedure
- Robotic stack (Da Vinci), ports, instruments, suture & dressings required to perform the procedure
- Outpatient & Inpatient provision

In addition, we will need:

- Research nurse & administrative support
- Additional blood sampling analysis and questionnaires during follow-up
- Analysis will be performed in-house by the Research Team with support from the University of Portsmouth if required (e.g. For statistical analysis).

19. DISSEMINATION AND OUTCOME

The study's findings will be written for publication for relevant high impact factor peer reviewed medical journals. Findings will also be submitted for presentation to high profile colorectal conferences such as the SAGES, ACPGBI, EAES and ESCP meetings.

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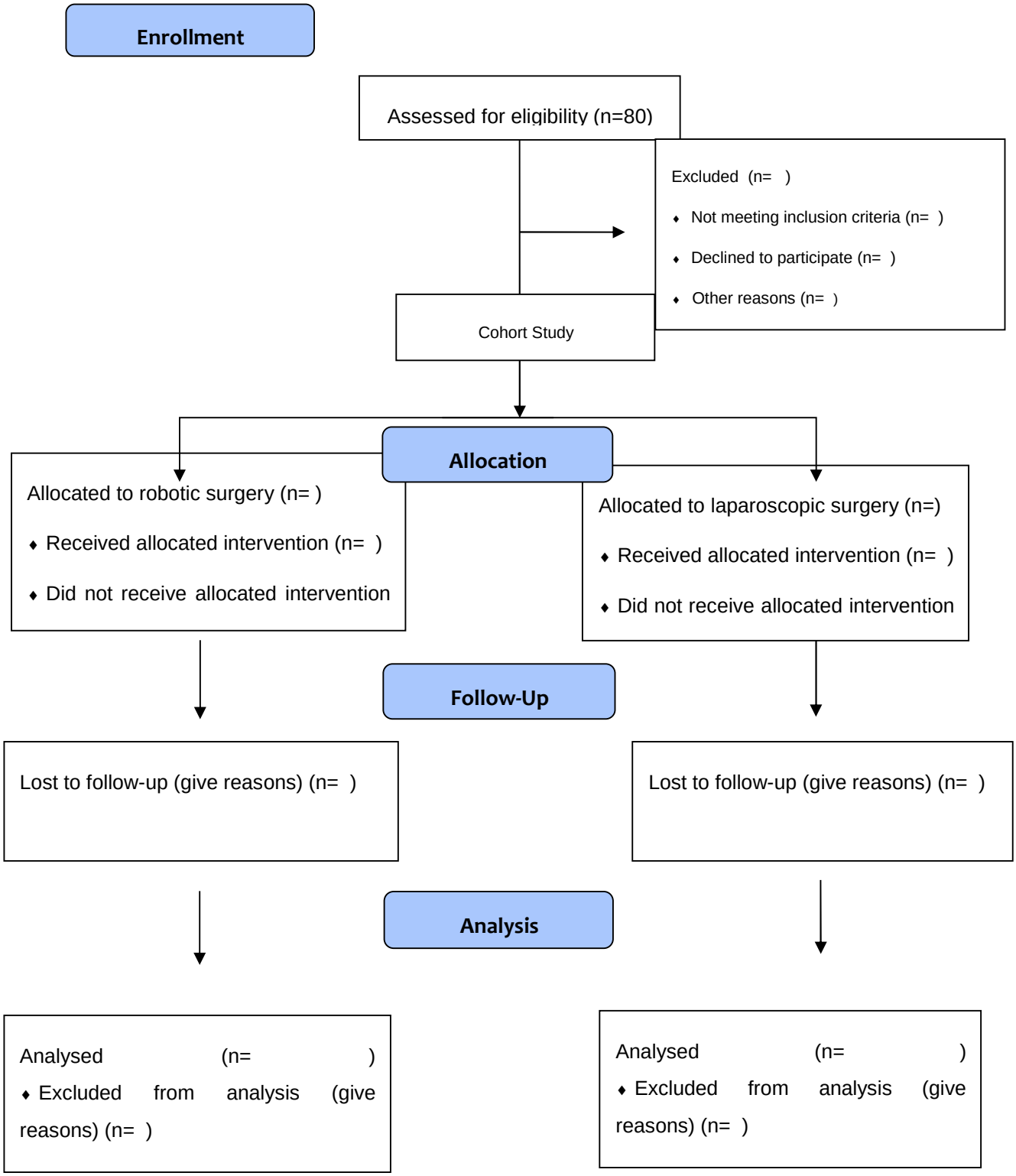
21. CONSORT 2010 FLOW DIAGRAM



22. APPENDIX 2 PARTICIPANT INFORMATION SHEET

23. APPENDIX 3 GP INFORMATION SHEET

24. APPENDIX 4 PATIENT ELIGIBILITY CHECKLIST

25. APPENDIX 5 INFORMED CONSENT FORM

26. APPENDIX 6 SAMPLE QUESTIONNAIRES

27. APPENDIX 7 SAMPLE DATA COLLECTION FORMS

28. APPENDIX 8 CONTRACTUAL AGREEMENTS WITH OUTSIDE CONSULTANTS / COLLABORATORS / INSTITUTIONS (E.G. INDUSTRY, CONTRACT RESEARCH ORGANISATIONS)