Health-Related Quality of Life and Survivorship in Locally Recurrent Rectal Cancer

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Intellectual Property and Publication Statements

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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NM developed the protocol with supervision from Galina Velikova (GV), Julia M. Brown (JMB), and Deena Harji (DH), conducted literature searches, data extraction, analysis, and manuscript writing. Ellen Ross (ER) contributed to the literature searches and data extraction. Fergus Houston (FH) undertook data extraction. GV, JMB, and DH, contributed to protocol development, interpretation of results, overall supervision of the project, and manuscript writing.

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NM undertook the data analysis which is described in chapter 4 of this thesis. DH led the development of the protocol, data extraction, analysis, and interpretation, and manuscript writing. Cherry Koh (CK) contributed to the data extraction and analysis. Ben Griffiths (BG) and Martyn Evans (ME) contributed to data extraction. Michael Solomon (MS) contributed to the protocol development, results interpretation, and manuscript writing. GV, JMB, and Peter Sagar (PS) contributed to the protocol development, results interpretation, manuscript writing, and project supervision.

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Abstract

Background

Growing interest in the impact of locally recurrent rectal cancer (LRRC) on health-related quality of life (HrQoL), resulted in the development of the LRRC-QoL patient-reported outcome measure (PROM), which has been validated for use in the UK. This thesis expands its utility through international validation, in addition to exploring long-term survivorship issues in LRRC.

Methods

There are three major components:

1) The quality of reporting of PROMs in LRRC: systematic review and a study comparing HrQoL in patients with primary rectal cancer (PRC) and LRRC.
2) International validation of the LRRC-QoL: validation in a cohort of patients from the UK and Australia, cross-cultural adaptation, external validation, and a prospective, multinational study of HrQoL in LRRC from diagnosis to 12-months.
3) Long-term survivorship in LRRC: mixed-methods study to identify long-term survivorship issues in LRRC.

Results

1) No studies reporting PROMs with evidence of content validity for use in LRRC were identified in the systematic review. Patients with LRRC reported worse HrQoL (FACT-C scores) than patients with PRC, further highlighting the need for a disease specific LRRC PROM and potential utility of registry data in reporting PROMs in this setting.
2) The LRRC-QoL demonstrated excellent psychometric properties in both the validation analysis of 117 patients and external validation analysis of 204 patients from 13 countries. Cross-cultural adaptation involved interviews with 67 patients

and produced versions for use in 9 new languages. HrQoL trajectories for 101 patients demonstrated worse HrQoL at 3- and 6-months in patients receiving treatment with curative intent.

3) Twenty-six patients participated in qualitative interviews, identifying eight survivorship themes, six (75%) of which are represented in the LRRC-QoL.

Conclusion

The LRRC-QoL measure is now internationally validated for use in 10 languages across 14 countries and its relevance to longer-term survivors of LRRC has been demonstrated. Future work will report full 12-month HrQoL trajectories for the patients recruited.

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List of Tables and Figures

Abbreviations

3D	3-dimensional
6MWT	6-minute walk test
ACPGBI	Association of Coloproctology of Great Britain and Ireland
ANOVA	Analysis of Variance
APER	Abdominoperineal Excision of the Rectum
AQOL	Assessment of Quality of Life
BMI	Body Mass Index
BPI	Brief Pain Inventory
BPOMS	Brief Profile of Mood States
CCG	Clinical Commissioning Groups
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
Ch2	Chi-squared
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
CONSORT-PRO	Consolidated Standards of Reporting Trials – Patient-Reported Outcomes
COPD	Chronic Obstructive Pulmonary Disease
CORECT-R	COloRECTal cancer Repository
COS	Core Outcome Set
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
COVID-19	Coronovirus disease caused by the SARS-CoV-2 virus
CPES	Cancer Patient Experience Survey
CRN	Clinical Research Network
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTIS	Clinical Trials Information System
CTT	Classical Test Theory
CTRU	Clinical Trials Research Unit
DIF	Differential Item Functioning
DIY	Do it Yourself

DPA	Data Protection Act
DWLS	Diagonal Weighted Least Squares
ECOG	Eastern Cooperative Oncology Group
EFA	Exploratory Factor Analysis
ELSiE	Extended Lateral pelvic Sidewall Excision
EORTC	European Organisation for Research and Treatment of Cancer
EORTC BR-SURV45	European Organisation for Research and Treatment of Cancer Breast Survivorship Module
EORTC CR-SURV34	European Organisation for Research and Treatment of Cancer Colorectal Survivorship Module
EORTC PR-SURV30	European Organisation for Research and Treatment of Cancer Prostate Survivorship Module
EORTC QLG	European Organisation for Research and Treatment of Cancer Quality of Life Group
EORTC QLQ-BLM30	European Organisation for Research and Treatment of Cancer Muscle Invasive Bladder Cancer Measure
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Measure
EORTC QLQ-CR29/ EORTC QLQ-CR38	European Organisation for Research and Treatment of Cancer Colorectal Module
EORTC SURV100	European Organisation for Research and Treatment of Cancer Survivorship Module
ePROM	Electronic Patient-Reported Outcome Measure
EQ-5D	EuroQoL measure of health-related quality of life
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
EQ-VAS	EuroQoL Visual Analogue Scale
ES	Effect Size
ESMO	European Society for Medical Oncology
EU	European Union
EMBASE	Excerpta Medica Database
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-C	Functional Assessment of Cancer Therapy – Colorectal Measure
FACT-C CCS	Functional Assessment of Cancer Therapy – Colorectal Measure Colorectal Cancer Subscale
FDA	U.S. Food and Drug Administration
FI	Faecal Incontinence
FLIC	Functional Living Index – Cancer

FSFI	Female Sexual Function Index
GDPR	General Data Protection Regulation
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRECCAR	Groupe de Recherche en Chirurgie du Rectum
HCP	Healthcare Professional
HES	Hospital Episode Statistics
HRA	Health Research Authority
HrQoL	Health-Related Quality of Life
ICC	Intraclass Correlation Coefficient
IIEF	International Index of Erectile Function
IMPACT	Improving the Management of Patients with Advanced Colorectal Tumours
IORT	Intra-Operative Radiotherapy
IQR	Inter-Quartile Range
IRB	Institutional Review Board
IRT	Item Response Theory
ISOQOL	International Society for Quality of Life Research
ISPOR	Professional Society for Health Economics and Outcomes Research
KMO	Kaiser-Meyer-Olkin
LAR	Low Anterior Resection
LARS	Low Anterior Resection Syndrome
LARC	Locally Advanced Rectal Cancer
LCCRT	Long Course Chemoradiotherapy
LEFS	Lower Extremity Functional Scale
LENT SOMA	Late Effects of Normal Tissue – Subjective, Objective, Management and Analytic
LRRC	Locally Recurrent Rectal Cancer
LRRC-QoL	Locally Recurrent Rectal Cancer – Quality of Life
MCID	Minimal Clinically Important Differences
MDT	Multi-Disciplinary Team
MID	Minimally Important Differences
MoU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging

MSKCC	Memorial Sloan Kettering Cancer Center
MSTS	Musculoskeletal Tumour Society Score
NATCAN	National Cancer Audit Collaborating Centre
NBOCA	National Bowel Cancer Audit
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NIHR	National Institute for Health Research
OID	Organisation Information Document
PCSP	Personalised Care and Support Planning
PE	Pelvic Exenteration
PIC	Patient Identification Centre
PIL	Patient Information Leaflet
PIP	Personal Independence Payments
POMS-SF	Profile of Mood States – Short Form
PPI	Patient and Public Involvement
PRC	Primary Rectal Cancer
PREM	Patient-Reported Experience Measure
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
PROMIS	Patient-Reported Outcomes Measurement Information System
PROSPERO	International prospective register of systematic reviews
PSFU	Personalised Stratified Follow Up
PubMed	Publisher Medline
QoL	Quality of Life
R0	Complete surgical resection
R1	Microscopic resection margin involvement
R2	Macroscopic residual tumour
R&D	Research and Development
RC	Rectal Cancer
RCS	Royal College of Surgeons of England
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMSEA	Root-Mean-Square-Error-of-Approximation

RoB 2	Risk of Bias in randomised trials revised tool
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions tool
SABR/SBRT	Stereotactic Ablative Radiotherapy/ Stereotactic Body Radiotherapy
SCRT	Short Course Radiotherapy
SD	Standard Deviation
SF-36	36-Item Short Form Survey
SF6D	Short Form Six-Dimension
SHIM	Sexual Health Inventory for Men
SIV	Site Initiation Visit
SRQR	Standards for Reporting Qualitative Research
SRM	Standardised Response Mean
SVQ	Sexual function – Vaginal changes Questionnaire
Sx	Symptoms
TLI	Tucker Lewis Index
TME	Total Mesorectal Excision
TNM	Tumour, Nodes, Metastases
TNT	Total Neoadjuvant Therapy
UK	United Kingdom
UKPEN	United Kingdom Pelvic Exenteration Network
USA	United States of America
VAS	Visual Analogue Scale
VNRS	Verbal Numerical Rating Scale
VRAM	Vertical Rectus Abdominis Myocutaneous flap

Chapter 1 Introduction

1.1 Locally Recurrent Rectal Cancer

Locally recurrent rectal cancer (LRRC), is defined as "*recurrence, progression or development of new sites of rectal tumour within the pelvis after previous resectional surgery for rectal cancer*" (1), and is a relatively rare occurrence. Rates have been consistently reported at 4-10% (2-6) following the introduction of Total Mesorectal Excision (TME) (3) for primary rectal cancer (PRC), coupled with improvements in both neoadjuvant treatment approaches (7, 8) and pre-operative imaging (9, 10). Though the incidence of LRRC has now remained low for decades, it continues to present a significant challenge to both patients and clinicians, given the impact of the disease and complexity of its management. Recent years have seen an amplified, international focus on improving outcomes in this specific group of patients, resulting in several important developments in the multi-disciplinary management of LRRC.

1.1.1 Multi-Disciplinary Management of LRRC

The treatment of LRRC is of a complex and highly specialist nature and the role of the multi-disciplinary team (MDT) is increasingly important both in the UK and internationally. The recent Association of Coloproctology of Great Britain and Ireland (ACPGBI) Improving the Management of Patients with Advanced Colorectal Tumours (IMPACT) Organisational Survey of colorectal cancer MDTs across the UK and Ireland reported that 22.2% of MDTs offer surgery for LRRC (11). However, more advanced techniques such as high sacrectomy above the level of the third sacral vertebra and complex vascular resection +/- reconstruction, were offered by 9.1% and 18.9% of MDTs

respectively (11). Internationally, there is increased centralisation of units offering ultra-radical surgery, with established national referral pathways for LRRC in countries such as Australia (12, 13), and regional referral pathways in France (14). The ACPGBI IMPACT Initiative has identified several priorities to address to improve the management of patients with advanced colorectal tumours in the UK and Ireland, including the development of specialist regional MDTs (15). There are limited published data regarding specialist MDTs in the UK, though a number of them now exist (16-19). Establishing specialist regional MDTs has several potential benefits. These include improving equality of access to specialist services both within and across different regions, and improving decision-making by ensuring all key stakeholders are involved in MDT discussions, such as hepatobiliary and thoracic surgeons, palliative care physicians, in addition to the makeup of a traditional colorectal cancer MDT (15). Centralisation of these services could also lead to higher volume caseloads, which is generally associated with improved outcomes across a range of surgical disciplines, including colorectal cancer surgery (20-24).

1.1.1.1 Developments in Surgical Management of LRRC

Surgical resection represents the mainstay of curative treatment for LRRC. Since its inception in the 1940s, exenterative surgery has entered the mainstream and boundaries have been pushed in the form of ultra-radical approaches (25). These include lateral pelvic compartment excision (26) or Extended Lateral pelvic Sidewall Excision (ELSiE) (27), sciatic and femoral nerve resections (28), iliac vessel resection (29), and high sacrectomy (30, 31). Specialist centres have amassed a wealth of experience in this area, reaching significant milestones in relation to the number of procedures performed (32). This advancement in surgical techniques has been furthered through the sharing of experience, knowledge and specific procedural steps, traditionally through publications such as those

describing the techniques highlighted, but more recently through video vignettes, facilitated by technological developments, such as smart glasses technology (33).

National and international collaboration within the surgical community, as described in relation to sharing surgical techniques, has been a major driving force in improving the management of LRRC. This has been aided by the establishment of collaborative initiatives including the PelvEx Collaborative, the Association of Coloproctology of Great Britain and Ireland's Improving the Management of Patients with Advanced Colorectal Tumours (ACPGBI IMPACT) Initiative, and the UK Pelvic Exenteration Network (UKPEN). The PelvEx Collaborative was formed in the late 2010s to provide large volume retrospective data from specialist centres undertaking pelvic exenteration, to develop future clinical trials and create guidelines for the treatment for locally advanced and recurrent rectal cancer (34). Since its establishment, PelvEx has gone on to publish a number of retrospective studies (34-38), systematic reviews (39, 40), guidelines using Delphi methodology (41-43), and has developed a randomised controlled trial (RCT) which is currently open to recruitment (44). The IMPACT initiative was established by the ACPGBI in 2017 in response to the optimisation of care for patients with advanced colorectal cancer being identified as a research priority (45). The first stage in the development of the IMPACT initiative was a priority setting exercise which identified nine key priorities to improve the management of patients with advanced colorectal tumours (15). These themes include current service provision, specialist services, communication, education, access to care, definitions and standardisation, research and audit, outcome measurement, and funding of specialist care (15). The IMPACT initiative went on to lead a programme of workshops, between 2018 and 2020, for colorectal MDTs to improve awareness and understanding of treatment options for patients with advanced cancer (15). Further work of the IMPACT initiative is currently

underway to identify UK-wide differences in decision-making and treatment strategies in all patients with advanced or recurrent rectal cancer (46). The UKPEN was established in 2020 as a network of UK-based healthcare professionals caring for patients with advanced and recurrent pelvic cancers, specifically to influence healthcare commissioning. This is pertinent given the significant healthcare expense associated with pelvic exenteration surgery (47). In relation to their work to date, UKPEN have published a statement related to the care of patients with advanced colorectal cancer during the COVID-19 pandemic (48), as well as a lexicon to standardise the terminology used to describe the operative components of pelvic exenteration surgery (49).

Developments in advancing surgical techniques, increased experience in relation to surgical decision-making (12), combined with advances in other aspects of care, such as peri-operative management (41), have led to significant improvements in clinical outcomes. Achieving a complete (R0) resection is strongly associated with increased survival (19, 35) and the proportion of patients in which this is achieved is now as high as 82.6% (32, 50, 51). Overall five-year survival rates of 34.5-44.6% have been reported in patients undergoing surgery (32, 50) and up to 63% following R0 resection (52-54). However, these survival outcomes are reported from a small number of highly experienced specialist units, PelvEx collaborative data from twenty-seven international specialist centres described a R0 resection rate of 55.4% and five-year overall survival of 28.2% following R0 resection (35).

High-quality radiological assessment is a central component of the MDT and in the planning of complex exenterative procedures with a view to achieving a R0 surgical resection (55). Recent developments related to the field of radiology include 3D

reconstruction to facilitate operative planning and understanding of complex anatomy (56). This technology is of considerable value in LRRC, given its complexity from an anatomical standpoint. Image-guided navigation is another development which could offer benefit in this setting. It has been reported as feasible (57), safe, and associated with increased R0 resection rates in LRRC (58), as well as being cost-effective (59). However, image-guided navigation has not been assessed in a RCT to date.

There are now relatively few absolute contraindications to surgery. Frailty, metastatic disease, and patient choice, represent the main reasons for patients not undergoing exenteration (60). A significant proportion of patients with LRRC present with synchronous metastatic disease, with reported rates of 41-44% (61, 62). This has traditionally been regarded as a barrier to curative surgical resection. However, specialist centres are increasingly employing treatment strategies that include radiofrequency ablation, stereotactic radiotherapy, or surgical resection for liver and lung metastases, in combination with radical surgery for LRRC, and reporting 3-year overall survival of up to 39% (63, 64). One of the central difficulties in treating patients with LRRC and metastatic disease is balancing the burden of aggressive treatment approaches against potential survival benefits and their impact on quality of life (QoL). There is very limited guidance regarding curative treatment strategies in patients with LRRC and metastases, and these strategies remain controversial (65). Current practice tends to focus on careful selection of patients who may benefit from this approach. Major frailty is likely to always be an absolute contraindication to exenterative surgery given the significant morbidity associated with these procedures, with reported rates of up to 60% (66-68). Poor preoperative fitness is associated with higher rates of postoperative complications (69, 70), and there is increasing focus on efforts to optimise patients' condition prior to surgery (71). The PRIORITY trial is currently underway to assess the role of prehabilitation prior

to exenterative surgery (72) and many specialist centres routinely undertake measures to optimise patient fitness where possible. The proportion of patients who decline exenterative surgery for LRRC reflects both the significant morbidity of these procedures and the importance of robust informed consent processes.

1.1.1.2 Developments in Oncological Treatment of LRRC

There is considerable complexity regarding oncological treatment strategies in patients with LRRC, as any treatment received for their primary disease becomes a factor within the decision-making process. Radiation therapy is particularly challenging in this specific patient group. One example of this is in the delivery of radiotherapy and delineation of the target volume. This can be challenging for several reasons, including previous surgery for PRC, with associated loss of normal anatomical planes, more frequent presence of invasion into surrounding structures, and fibrosis associated with previous radiotherapy. Delineation guidelines have now been developed to reduce inter-observer variability (73). One of the central challenges in radiation therapy for LRRC relates to the significant proportion of patients presenting with LRRC with a history of previous pelvic radiotherapy. The use of pelvic re-irradiation has been a divisive treatment strategy due to concerns about cumulative toxicity and late effects of treatment, particularly the risk of bowel toxicity and this limiting dose. In some centres internationally, re-irradiation for LRRC has been described as standard practice for a number of years (74, 75), with acceptable reported rates of toxicity (76-80). Current international guidelines from both PelvEx and the European Society for Medical Oncology (ESMO) do not advocate the routine use of re-irradiation, acknowledging its potential to help achieve a R0 resection in selected patients (43, 81) or for symptom palliation (81).

High-quality evidence regarding the use of re-irradiation in LRRC is required to inform practice. To date there has been a lack of clinical trial data, likely due to the challenges associated with conducting RCTs in this setting. Patients with LRRC are a relatively rare and heterogenous group and therefore issues such as recruitment and standardisation of treatment arms present significant difficulties. However, two RCTs are now underway; firstly, the GRECCAR 15 trial, which compares neoadjuvant (induction) chemotherapy followed by re-irradiation with neoadjuvant chemotherapy alone in patients with LRRC who have previously received radiotherapy (82). As described, one of the central roles of neoadjuvant treatment for LRRC is to increase the likelihood of achieving a R0 resection and this serves as the primary endpoint of the trial (82). Secondly, the PelvEx II trial, also currently open to recruitment, compares induction chemotherapy followed by neoadjuvant chemoradiotherapy (including re-irradiation) to neoadjuvant chemoradiotherapy alone, with a primary endpoint of R0 resection rate (44). The results of these two trials are likely to shape future practice regarding neoadjuvant therapy for LRRC.

Current pelvic re-irradiation practice remains variable internationally and was only relatively recently commissioned by National Health Service (NHS) England for routine use in the form of stereotactic ablative radiotherapy (SABR) (83). In relation to LRRC, SABR was commissioned as a palliative treatment modality for patients with inoperable disease, or for use in patients with a positive surgical margin. SABR delivers high, targeted doses of ionising radiation with adjacent tissues receiving a much lower dose, thereby reducing the risk of injury to surrounding structures. Johnstone et al. have reported a case series of 69 patients receiving SABR for LRRC, with a median progression free survival of 12.1 months and median overall survival of 38.7 months (84). These results compare favourably to patients undergoing a R2 (macroscopically positive)

resection with reported median survival of 16 months (35). SABR re-irradiation has been reported to be well-tolerated across a range of pelvic malignancies, with improved local disease control (85). The UK SABR Consortium are currently conducting a national prospective audit of pelvic SABR re-irradiation to inform treatment decisions at an individual patient level, optimising SABR re-irradiation practice, and helping to design future clinical trials in this area (83).

In the context of rectal cancer treatment, total neoadjuvant therapy (TNT) involves the addition of chemotherapy either prior (induction) or following (consolidation) chemoradiotherapy in a neoadjuvant setting. Chemotherapy has previously been delivered predominately in an adjuvant setting following surgical resection for rectal cancer, with a view to reducing the risk of distant disease failure and improving survival outcomes (86). TNT was introduced to PRC management to treat micrometastatic disease and reduce rates of distant metastases/disease failure. Clinical trials have reported higher rates of pathological complete response (87) and reduced rates of distant treatment failure (88) in patients receiving TNT and it is recommended by the National Comprehensive Cancer Network (NCCN) as the preferred approach for stage II-III PRC (89). In relation to LRRC, induction chemotherapy is standard practice in selected centres internationally, it has not been demonstrated to increase disease-free survival, though was associated with an increased rate of pathological complete response in a single-centre retrospective cohort analysis (90). TNT is not currently recommended for use in LRRC given the insufficient evidence to suggest a significant benefit (43). Both the GRECCAR 15 and PelvEx II trials include the addition of induction chemotherapy to neoadjuvant regimes and will therefore evaluate the role of TNT in LRRC in addition to re-irradiation (44, 82).

The use of radiotherapy in LRRC is not limited to neoadjuvant or palliative settings and can also be administered intra-operatively. Intra-operative radiotherapy (IORT) is considered routine practice in some centres and used in combination with re-irradiation in patients at risk of a R1 resection, or to attempt organ preservation with closer margins (75). IORT is endorsed by international guidelines for use in cases with threatened margins during surgery with a view to reducing re-recurrence rates (43). IORT can be administered in different forms, through electron beam therapy or through high-dose-rate intraoperative brachytherapy. High-dose-rate intraoperative brachytherapy has been shown to potentially increase local recurrence-free survival in patients with an R1 resection when compared with electron beam IORT (91), suggesting that higher doses may convey additional benefit. However, the reported rate of major postoperative complications was higher in patients receiving high-dose-rate intraoperative brachytherapy (91). The ELECTRA trial is currently underway to investigate the feasibility of recruiting patients with locally advanced rectal cancer (LARC) and LRRC with predicted narrow or close surgical margins, to a RCT of IORT (92). The trial includes three treatment arms of extended margin surgery along, surgery including IORT at standard dose, or surgery including IORT at higher dose (92), and will offer additional information regarding the role of IORT in LARC and LRRC.

1.2 Patient Reported Outcomes in LRRC

Patient-reported outcomes (PROs), are defined as "*a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's responses by a clinician or anyone else*" (93). Health-related quality of life (HrQoL) is one of the most commonly

reported PROs and communicates the impact of a persons' health, medical condition, or treatment of a medical condition on their QoL; "*most conceptualisations of HrQoL include the dimensions of physical functioning, social functioning, role functioning, mental health, and general health perceptions*" (94). PROs such as HrQoL can offer a patient-focused view of the impact of a disease, treatment, or intervention, which is of significant value to patients when considered alongside traditional clinical outcomes (15). This is particularly pertinent in LRRC where both the disease itself and its treatment are associated with significant morbidity.

Patient reported outcome measures (PROMs) are the tools through which PROs are assessed and reported. PROMs can be designed as disease-specific or generic, for instance, a generic PROM measure concepts which are broadly relevant to a large number of people. One of the main advantages of generic PROMs is that they can be used in different groups of patients and even on a population level, allowing for comparison across groups. Disease-specific PROMs measure concepts relevant to a specific group of patients with a particular condition, they are more sensitive to changes in disease burden or health status than generic PROMs. However, to be considered valid in a specific group of patients, both disease-specific and generic PROMs should be shown to have content validity in that specific group of patients. Content validity being "*the degree to which the content of a PROM is an adequate reflection of the construct to be measured*" (95). Generic and disease-specific PROMs are frequently used together, and this modular approach is endorsed by the European Organisation for Research and Treatment of Cancer quality of life group (EORTC QLG) through combining the core cancer module (EORTC QLQ-C30) with a site-specific module, such as the Colorectal Cancer Module (EORTC QLQ-CR29). More recently, the development of PRO item libraries has allowed

for a more flexible, customisable approach to PRO assessment through the selection of specific items or multi-item scales for use in a specific context (96).

1.2.1 Current Reporting of PROs in LRRC

The significant developments in the management of LRRC described above suggest that perhaps we are now approaching the upper limits in terms of the extent of surgical resection that can be offered from an anatomical perspective (25, 65). Focus appears to be shifting towards balancing these procedures against their impact on the patient, particularly in relation to their QoL (97), and is apparent in the increasing volume of literature regarding PROs in LRRC. Reporting PROs in LRRC and its management is particularly important given that it can offer a more holistic viewpoint of these ultra-radical procedures and complex treatment pathways. This is reflected in the studies reported to date which predominately include patients undergoing surgery with curative intent and focus on HrQoL. Current evidence suggests that overall HrQoL decreases following exenterative surgery, recovering to or beyond baseline at 6-9 months (97). The achievement of a R0 resection is associated with improved HrQoL outcomes (97) and baseline HrQoL has been demonstrated to be a predictor of QoL post pelvic exenteration in patients with LRRC (98).

The different components of HrQoL have also been interrogated in relation to PROs reported in patients undergoing pelvic exenteration for advanced pelvic malignancy, including LRRC (99). This includes physical function, role function, sexual function, and body image, which were reported to decrease 3-6 months post-surgery, whereas psychological function was relatively stable (99). The impact of radical surgeries on HrQoL and functional outcomes have also been reported (28, 100). This includes sciatic

and femoral nerve resection, demonstrating a significant reduction in physical function at 6-months, returning to baseline by 12-months (28). In relation to functional outcomes, 96% of patients who had undergone complete sciatic nerve resection and 92% of patients who had undergone partial sciatic nerve resection were able to mobilise independently with or without a walking aid (28). HrQoL has also been reported in patients undergoing sacrectomy in association with pelvic exenteration, with patients undergoing sacrectomy experiencing worse physical function (100). In relation to level of sacrectomy, patients who underwent high sacrectomy had significantly worse lower limb function, physical function, and mental health scores when compared with low sacrectomy (100).

PROs in patients receiving treatment for LRRC with palliative intent are less well reported. Palliative surgery for LARC and LRRC is controversial given it is not associated with improved survival outcomes, and has not been demonstrated to improve HrQoL, with high rates of post-operative morbidity (39, 101). However, a PelvEx systematic review identified 509 patients who had undergone palliative exenteration, reporting that up to 79% of patients experienced some form of symptom-relief (39). In relation to patients receiving non-surgical palliative treatment, cross-sectional HrQoL outcomes have been reported and compared with patients receiving curative surgical treatment for LRRC and demonstrate that patients receiving treatment with palliative intent reported worse overall short-term HrQoL (102). These patients also reported significantly worse social, emotional, and functional wellbeing, but experienced a lower burden of pelvic symptoms such as urinary frequency and incontinence (102). In relation to the type of treatment received, palliative chemoradiation was associated with worse HrQoL scores and higher symptom burden of frequency of defaecation compared with palliative chemotherapy (102).

Insights from a patient care perspective have been greatly aided by the growing body of literature related to PROs in LRRC. However, these can only be realised with the availability of high-quality evidence and if the PROMs being used to report outcomes have been robustly developed and validated. There are several important limitations to the current evidence regarding PROs in LRRC from a methodological standpoint which have been highlighted across previous reviews (39, 97, 103-105). These include heterogeneity of the patients included in studies of HrQoL in LRRC, with outcomes frequently being reported in combined cohorts of patients with primary and recurrent disease (97, 103-105), the majority of studies being retrospective in nature (104), heterogeneity in the use of comparator groups (97, 103) and the evidence generally being of low quality (39, 103-105). Denys et al.'s review focuses on patient-centred outcomes following pelvic exenteration for colorectal cancer, including both primary and recurrent disease (105). They described the use and timing of PROs in this setting, identifying the PROMs currently being used and again notes the high degree of heterogeneity (97, 103). They reported that the impact of urinary complications, discomfort or pain on sitting, and functional disability are inadequately represented, and that the broad range of questionnaires in use renders comparison of outcomes across studies difficult (105).

Another major limitation is the apparent lack of PROMs developed and/or validated specifically for use in LRRC (104). Validity is the degree to which a PROM measures the construct it purports to measure (95). In assessing HrQoL in LRRC, a PROM can only be considered valid if there is evidence that it has been developed with input from patients with LRRC and provides a comprehensive assessment of HrQoL as the construct of interest, meaning that all aspects of HrQoL that are relevant to patients with LRRC are included. It is unclear whether PROMs such as the EORTC QLQ-CR29 and Functional Assessment of Cancer Therapy – Colorectal Measure (FACT-C), which are commonly

used to report PROs in LRRC, can be used reliably and validly in this specific cohort of patients. Undertaking a systematic review to identify the PROMs currently being used to report outcomes in LRRC and assessing their quality against existing guidelines would further the understanding of the overall quality of reporting of PROs in LRRC and identify areas for future work.

The lack of disease-specific measures for use in LRRC was identified by Harji et al. (104) and led to the development of the Locally Recurrent Rectal Cancer – Quality of Life (LRRC-QoL) questionnaire as a disease-specific measure of HrQoL for patients with LRRC. This measure was developed initially through the creation of the LRRC-QoL conceptual framework via a systematic review to identify HrQoL issues in LRRC (104) and qualitative patient interviews to establish HrQoL issues and themes (106). The HrQoL issues identified included symptoms, sexual function, psychological impact, role functioning, future perspective and issues relating to health service delivery and utilisation (106). PROMs which had been developed and validated for use in PRC were identified and assessed against International Society for Quality of Life Research (ISOQOL) standards (107) and the LRRC-QoL conceptual framework. The lack of overlap between existing PROMs and the LRRC-QoL conceptual framework supported the need for a disease-specific PROM for LRRC (108). The resultant development of the LRRC-QoL consisted of a process of item generation, pre-testing, and field testing to ensure its validity (108). The final field-testing phase consisted of a cross-sectional observational cohort study: patients were recruited from 5 UK and 2 Australian sites, with the intention to recruit 160 patients in total. A preliminary psychometric analysis was undertaken consisting of 80 patients recruited from the UK. Australian patients were not included at this time as recruitment was ongoing (108). The analysis was limited by a small sample size without the Australian cohort and due to missing data. However, the

results demonstrated that the LRRC-QoL had good construct validity, reasonably good convergent validity and unidimensionality of the scale structure, with the majority of the LRRC-QoL scales found to be reliable (108). The results of the field testing in the UK support the LRRC-QoL as a valid measure of HrQoL for use in British patients.

Although the lack of disease-specific measures utilised to date in reporting PROs in LRRC is a significant limitation (104), existing data may still have value in defining the impact of LRRC and its treatment on HrQoL. Many of the measures previously identified in reporting outcomes in LRRC are either generic measures or disease-specific measures designed for use in primary colorectal cancer, such as the EORTC QLQ-CR29 and FACT-C (97, 103-105).

1.2.2 Future Developments Regarding Reporting HrQoL in LRRC

As highlighted, the development of the LRRC-QoL represented a significant advance in the reporting of HrQoL in LRRC (108). Refining a PROM is an ongoing process, disease-specific PROMs in particular should be continually reviewed and updated to reflect any significant changes in the management of the disease (109). There are a number of developments which could further refine and expand the utility the LRRC-QoL. These include cross-cultural adaptation, external validation, the development of an online version or ePROM, and the calculation of minimally important differences (MIDs).

1.2.2.1 Cross-Cultural Adaptation

The cross-cultural adaptation of a PROM is a process through which it is translated and/or adapted for use in different countries, languages, and cultures. A central requirement of this process is to ensure conceptual equivalence across different versions of the

questionnaire; enabling pooling of responses obtained from different language versions of the measure. The value of international collaboration is evident in relation to reporting and improving outcomes in LRRC. Undertaking cross-cultural adaptation of the LRRC-QoL will increase its generalisability and enable collection of international, disease-specific HrQoL data.

There are several guidelines relating to the translation and cultural adaptation of PROMs (110-112) which are summarised in Table 1.1. As demonstrated, the overall processes are broadly similar across the different guidelines. However, some aspects vary, such as the number of patients advised for inclusion in cognitive interviews, with some guidelines not advising on specific numbers and others ranging from at least 5 to 10-15. The methodological approach to cross-cultural adaptation of the LRRC-QoL, detailed in chapter 5, will be informed by the EORTC guidelines (110), in keeping with the original development of the LRRC-QoL. One of the main challenges anticipated in applying this approach is achieving the advised sample size for cognitive interviews of 10-15 patients per version of the measure, given that LRRC is relatively rare.

Table 1.1: Translation and cultural adaptation guidelines

EORTC (110)	ISPOR (112)	FDA (93)	COSMIN (113)	ISOQOL (107)	PROMIS (114)
Translation Procedure **1. Preparation Stage** All translations must be performed and finalised with consent from the EORTC Translation Unit. **2. Forward Translations** The forward translation step requires two separate, independently done translations from English into the target language. The translations should be done by native speakers of the native language with a very good command of English. They do not have to be professional translators. **3. Reconciliation** The two forward translations are reconciled into one by either the	**Translation and Cultural Adaptation** **Step 1 Preparation** Obtain permission to use instrument. Invite instrument developer to be involved. Develop explanation of concepts in instrument. Recruit key in-country persons to the project. **Step 2 Forward Translation** Development of at least two independent forward translations. It is preferable that one forward translation be carried out by the key in-country person. Provision of explanation of concepts in the instrument to the key in-	**Translation and Cultural Adaptation** A. Process used to translate and culturally adapt the instrument for populations that will use them in the trial. B. Description of patient testing, language- or culture-specific concerns, and rationale for decisions made to create new versions.	**Translation Process** 1. Describe both the original language in which the PROM was developed, the source language (if different from the original language) and the language in which the PROM will be translated. 2. Ensure that the items will be translated forward and backward. 3. Ensure that both forward translators have a mother tongue in the target language in which the PROM will be translated. 4. Ensure that one of the forward translators has expertise in the diseases involved, and I the construct measured by the PROM; the other forward translator is	**Minimum Standards for Translation of a PROM** A PROM translated to one or more languages should have documentation of the methods used to translate and evaluate the PROM in each language. Studies should include evidence from qualitative methods (e.g., cognitive testing) to evaluate the translations.	**Translation and Cultural Adaptation** All items, item context(s), and answer options are translated using the Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology (111). **1. Two simultaneous forward translations** Source items in English are translated into target language by two independent professional translators who are native speakers of the target language. **2. Reconciled single target language translation** A third independent translator, also a native speaker of the language, also a native speaker of the target language, reconciles the two forward translations by selecting one of

translation coordinator or a third translator. **4. Back Translations** The reconciled translation is translated back into English by two translators working independently of one another. Optimally they should be native speakers of English. **5. Back Translation Report** The back translation report should include all five translations. All changes to the pre-translated items should be marked and explained. **6. Proofreading** The preliminary translation is sent to a professional proof-reader for review. **7. Pilot-Testing**	country persons and forward translators. **Step 3 Reconciliation** Reconciliation of the forward translations into a single forward translation. Reconciliation decisions should be reviewed or referred to the project manager. **Step 4 Back Translation** Back translation of the reconciled translation into the source language. **Step 5 Back Translation Review** Review of the back translation(s) against the source language. This should be carried out by the project manager. **Step 6 Harmonization**	C. Copies of translated or adapted versions. D. Evidence that content validity and other measurement properties are comparable between the original and new instruments.	naïve on the construct measured by the PROM. 5. Ensure that both backward translators have a mother tongue in the original or source language. 6. Ensure that both backward translators are naïve in the disease involved and the construct to be measured. 7. Ensure that the translators will work independently from each other. 8. Provide a clear description on how the differences between the original and translated versions will be resolved. 9. Ensure that the translation will be reviewed by a committee (including the		the forward translations, creating a hybrid version, or providing a new version. **3. Backward translation** The reconciled version is then back-translated by a native English-speaking translator who is fluent in the target language. The translator does not see the original source items. **4. Back-translation review** The translation project manager compares source and back-translated English versions to identify discrepancies. **5. Expert reviews** Three experts who are native speakers of the target language, independently examine all of the preceding steps and select the most appropriate translation for each item.

The translated questionnaire should be pilot tested on a group of patients in order to check its comprehensibility in the target language. The group should comprise **10–15 patients** who belong to the population that is the target of the questionnaire. **8. Final Translation** The final translation is sent to the translation coordinator for final approval. **<u>Cultural Adaptation</u>** The cultural adaptation procedure applies to languages which are spoken in more than one country or as variants. As a general rule, no cultural adaptations of the English version are possible, and the English questionnaire is to be used in one form in all English-speaking countries and populations.	Harmonization of all new translations with each other and the source version. **Step 7 Cognitive Debriefing** The newly translated measure should be tested for cognitive equivalence by the key in-country person (or another in-country consultant) on a group of **5 to 8 respondents** in the target country. Respondents should be native speakers of the target language who adequately represent the target population (sex, age, education, diagnosis). **Step 8 Review of Cognitive Debriefing Results and Finalization** The review should be carried out by the project manager.		original developers of the PROM). 10. Write a feedback report of the translation process. 11. Perform a pilot study (e.g., cognitive interview study) to check the relevance of each item to the patients' experience, the comprehensiveness and comprehensibility of the PROM and the PROM instructions, items, response options, and recall period. 12. Perform the pilot study in a patient population representing the target population.		**6. Pre-finalization review** The translation project manager evaluates the reviewer's comments. **7. Finalization** A Language Coordinator determines the final translation by reviewing all the information and addressing the translation project manager's comments. **8. Harmonization and quality assurance** The translation project manager makes a preliminary assessment of the accuracy and equivalence of the final translation by comparing the final back-translations with the source. **9. Formatting, typesetting, and proofreading** Two proof-readers work independently.

1. Review of the existing translation The translation coordinator prepares a report including all items that in their opinion require changes. **2. Further processes** The further process of cultural adaptation is identical to steps 6–8 of the standard translation procedure.	**Step 9 Proofreading** The key in-country person and/or a proof-reader checks the final translation for spelling, diacritical, grammatical, or other errors. **Step 10 Final Report** The project manager writes the final report.				**10. Cognitive testing and linguistic validation** The goal is to have each new item debriefed in the target country **by at least 5 participants** in a cognitive debriefing interview. **11. Analysis of participants' comments and finalization of translation** The translation project manager compiles participants' comments and summarizes the issues.

Red text is used to highlight the number of patients advised for cognitive interviews.

1.2.2.2 External Validation of the LRRC-QoL

External validation involves undertaking a psychometric analysis of a PROM in a different cohort of patients to those involved in the original PROM development. It is an important process in establishing the reproducibility and generalisability of a PROM and its psychometric properties. The psychometric analysis to validate the LRRC-QoL in a UK cohort highlighted the need to undertake further analyses to confirm the reliability of the scales, convergent validity, known groups validity, and responsiveness of this measure. Undertaking external validation in a larger, separate cohort of patients is central to confirming these psychometric properties and is described in chapter 6 of this thesis.

Given the rare and advanced nature of LRRC, recruiting a large cohort of patients with LRRC to enable external validation of the LRRC-QoL, is likely to be particularly difficult. The original LRRC-QoL validation study reported a response rate of 38.8% (108), and studies measuring HrQoL in similar settings, such as metastatic disease, have also reported recruitment rates of around 40% (115, 116). Challenges encountered during the development of the LRRC-QoL included: delays in obtaining local Research and Development approvals from NHS sites, delays in obtaining Australian Ethics Committee and local ethics committee approvals in Sydney and Melbourne, competing studies at the Australian centres, small recruitment pools due to the rarity of LRRC, and low response rates (108). These issues are all anticipated to apply to future work regarding the LRRC-QoL and therefore strategies including centralised co-ordination of follow-up, co-enrolment, and potential adoption into current trials and registries will all be considered. Since the original development of the LRRC-QoL there are additional external factors which are likely to impact this work, including Brexit and the COVID-19 pandemic.

Reporting prospective QoL outcomes in LRRC using a validated measure would offer several benefits in both clinical and academic settings. As demonstrated by Harji et al., QoL trajectories can be a useful adjunct to discussions with patients regarding their treatment, particularly through the visual representation of this data (99). Prospective HrQoL datasets offer additional avenues for further enquiry, the availability of such data led to the identification of HrQoL as a prognostic factor for overall survival in patients with metastatic colorectal cancer (116, 117), in addition to identifying baseline QoL as a predictor of QoL following pelvic exenteration in patients with LRRC (98).

1.3 Survivorship in LRRC

The concept of cancer survivorship is somewhat disputed, the most widely used definition being "*a process that begins at the moment of diagnosis and continues through the balance of life*" (118). However, a cancer survivor has also been defined as a person who has completed treatment with curative intent and remains disease-free (119). Even considering the range of definitions in use, there are undoubtedly increasing numbers of LRRC survivors following developments in the management of LRRC and associated improved survival outcomes. The rising number of LRRC survivors has important implications from patient, clinician, and healthcare service provision perspectives.

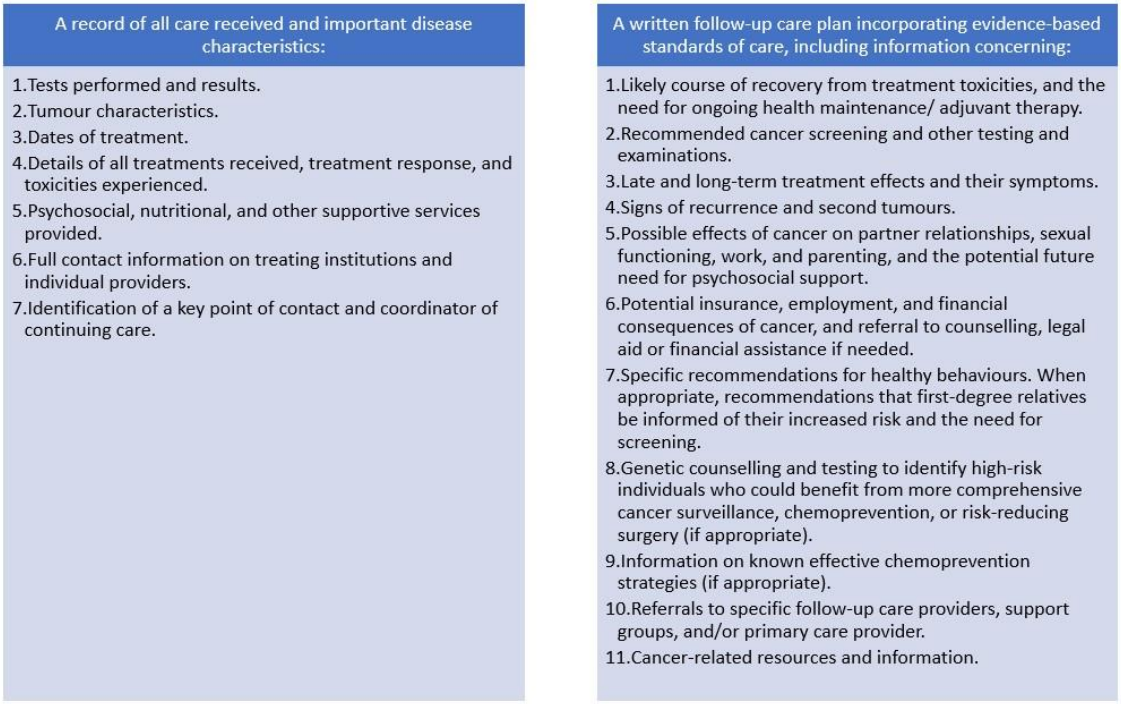
1.3.1 Cancer Survivorship and Survivorship Issues

General improvements in cancer survival rates, as a result of earlier detection and advances in treatment (120), have prompted greater focus on survivorship across the cancer care continuum. Cancer survivorship is a process which encompasses experiences

and issues which affect patients living with and beyond cancer, namely cancer survivorship issues. Survivorship issues represent the range of issues that are relevant to cancer survivors, including late effects of treatment and HrQoL (119). PROMs measuring HrQoL are typically developed in patients experiencing acute symptoms related to their cancer diagnosis and treatment, which may not be relevant to longer-term survivors (119). Late and long-term effects of cancer and its treatment vary for different types of malignancy and treatments. Common survivorship themes across a number of different malignancies include: physical, psychological and social burden, surveillance, the risk of recurrence, increased morbidity, and long-term mortality (121). Cancer survivors therefore experience a unique set of healthcare needs in addition to those that accompany increasing age, such as the development of co-morbidities and physical limitations. These issues have an impact from a patient perspective on their HrQoL and from a healthcare service perspective in the provision of patient-centred care for cancer survivors, an issue which is only set to increase in coming years.

The need to provide additional targeted support for cancer survivors has been highlighted by several organisations including the Institute of Medicine in their landmark 2006 report which advocated the use of survivorship care plans, provided at the point of hospital discharge and containing the information detailed in Figure 1.1 (120). However, awareness of resources such as survivorship care plans from a clinician perspective and their implementation remain suboptimal (122, 123), with reported barriers including resources from both a time and financial standpoint (124).

Figure 1.1: A summary of the Institute of Medicine's minimum contents advised for inclusion in Survivorship Care Plans (120)



Different frameworks of survivorship care needs have been identified with considerable overlap (125, 126). ESMO describe five main components of survivorship care, including 1) physical effects of cancer and chronic medical conditions, 2) psychological effects of cancer, 3) social, work, and financial effects of cancer, 4) surveillance for recurrences and second cancers, and 5) cancer prevention and overall health and wellbeing promotion (126). Delivery of survivorship care continues to present challenges, particularly in the integration of care between primary and secondary or even tertiary providers, in addition to an overreliance on specialist-led follow-up which is not cost-effective and potentially unsustainable in the context of predicted global health workforce shortages (127, 128). Different approaches to survivorship care delivery include primary care models, shared-care between primary care and secondary/tertiary care providers, dedicated survivorship clinics, nurse-led approaches, and supported self-management (126, 128).

The routine collection of PROs and unmet needs within survivorship care settings is also advocated (125, 126, 129). The potential benefits to be gained from integrating PROs within clinical care have been described (130-132) and are likely to extend to a survivorship setting. As previously highlighted, there are several challenges related to integrating these systems within existing NHS care pathways, posing a significant barrier to their widespread uptake. In low and middle-income countries, remote symptom monitoring may be particularly beneficial where access to services can be limited and costly for patients (133). In recent years the EORTC QLG have developed HrQoL assessments to capture issues relevant to disease-free cancer survivors both overall (EORTC SURV100) and for specific sites including breast (BR-SURV45), colorectal (CR-SURV34), and prostate cancer (PR-SURV30) (134). In this context, survivors were considered as patients being disease-free and at least one year post treatment (119). These measures can be used to report HrQoL prospectively long-term both in clinical and academic settings. The inclusion of scales from the EORTC QLQ-C30 within the EORTC SURV100 offer continuity in HrQoL assessment as patients transition from completing the core module to the survivorship module at 12-months (134).

1.3.2 Current Evidence Regarding Survivorship in LRRC

The increasing interest in cancer survivorship has extended to patients with colorectal cancer. Survivorship issues have been widely reported in primary colorectal cancer and reflect the common themes described for cancer survivors (121). Issues identified which are more specific to primary colorectal cancer and its treatment include: bowel dysfunction, stoma-related issues, sexual dysfunction, peripheral neuropathy secondary to oxaliplatin chemotherapy, and negative body image (135-138). The ACPGBI 2017 guidelines recommend that individualised care planning, treatment and follow-up should be developed for colorectal and anal cancer survivors (139). However, a number of unmet

needs have been reported in current colorectal cancer follow-up, including: psychological and social support and a lack of information related to chronic complications of treatment, such as peripheral neuropathy, bowel dysfunction, and sexual dysfunction, in addition to a lack of dietary advice (140, 141).

In terms of patients with advanced and recurrent colorectal cancer, survivorship issues have been less widely reported. Lim et al. have recently produced a volume of work exploring survivorship in patients with advanced and recurrent disease up to 2 years from diagnosis or surgery (142-145). Across a series of manuscripts, Lim et al. have explored experiences and survivorship issues (143), employment and finances (145), fear of disease progression or recurrence (142), and healthcare experiences (144) in this group of patients. They identified a number of physical and psychosocial issues experienced by patients, including post-surgical complications, reduced mobility, bowel dysfunction, challenges associated with stomas, issues related to chemotherapy such as peripheral neuropathy and fatigue, impact on relationships, and changes in personal identity (143). Notably, patients experiencing a long and slow recovery process following pelvic exenteration reported worse QoL (143). Challenges related to the complex management of advanced and recurrent colorectal cancer were also identified, including issues related to receiving treatment across different specialties and hospitals (143, 144). Survivorship care plans and survivorship clinics were proposed as potential solutions to some of the issues experienced in current follow-up care, particularly in relation to the provision of information (144).

The literature regarding longer term survivorship issues and unmet needs is particularly limited in LRRC, likely due to long-term survivors being historically low in number.

Existing evidence is largely focused on long-term HrQoL with the majority of results reported from a single centre with significant experience in this area (146, 147). Though survivorship issues are not well reported in LRRC, some long-term and lasting effects of treatment have been identified. As described, procedures including sciatic or femoral nerve resection and sacrectomy are associated with chronic complications including foot drop and impaired mobility (28, 100). Empty pelvis syndrome is another chronic complication of pelvic exenteration surgery. Empty pelvis syndrome has been described as a collection of issues that include perineal wound breakdown, perineal herniation, and complex perineal fistulas, which can occur in relation to the pelvic void created by surgery (148). A recent study has reported that 6% of patients required reoperative abdominal or perineal procedures for empty pelvis syndrome following pelvic exenteration for advanced or recurrent pelvic malignancy (149). Long-term urological complications, such as urinary leak or fistula, were also identified as a common reason for reoperation (149). These chronic complications requiring re-intervention are all likely to impact on patients' HrQoL.

1.3.3 Future Directions Regarding Survivorship in LRRC

The survivorship work of the EORTC QLG shows that a significant proportion of the issues included in measures designed to assess HrQoL in patients with cancer are no longer relevant to survivors after 12 months (119). The LRRC-QoL was developed for use in patients who were within 2 years of diagnosis of LRRC and therefore the majority of this patient group were in the acute treatment phase (106, 108). It is possible that longer term LRRC survivors experience different issues, which may not be captured by the LRRC-QoL measure. The identification of survivorship issues and unmet needs in current LRRC survivorship care pathways could be used to improve follow-up and survivorship care, including the development of targeted interventions. Identifying the survivorship

issues relevant to long-term survivors of LRRC will also help in determining whether additional measures are required to support HrQoL assessment in this group of patients.

1.4 Summary

There are evidently several areas for further research regarding HrQoL in patients with LRRC. In relation to reporting HrQoL in LRRC, key areas for future work relate to interrogating the quality of current reporting of PROMs and the ongoing development of the LRRC-QoL. Where the quality of reporting PROMs in LRRC is concerned, this includes identifying the existing PROMs being used to report outcomes in LRRC, establishing the overall quality of reporting, and examining whether the PROMs currently in use should continue to be used to report HrQoL in LRRC. In relation to the ongoing development of the LRRC-QoL measure, this includes reporting a psychometric analysis in a combined UK and Australian cohort, cross-cultural adaptation, external validation, and utilising the LRRC-QoL to report HrQoL prospectively in LRRC. In terms of understanding survivorship in LRRC, the HrQoL and survivorship issues relevant to patients up to 2-years from diagnosis or post-surgery for LRRC have been previously documented (106, 143). However, the experiences of longer-term survivors remain underreported and represent an important area of future work.

1.4.1 Hypothesis

There were three research hypotheses in this thesis, related to HrQoL in LRRC:

1. There was a perception that existing evidence regarding HrQoL in LRRC is low in quality and reported utilising PROMs which have not been adequately developed or validated for use in this context.

2. The LRRC-QoL could be used on an international platform as a disease-specific measure of HrQoL,
3. There is a lack of evidence describing longer term survivorship in LRRC and the experiences and issues relevant to this patient group are likely to be different to those of patients undergoing treatment.

1.4.2 Aims

The overarching aims of this thesis are to improve the quality of measurement and reporting of HrQoL in LRRC, including identification of the survivorship issues relevant to long-term survivors of LRRC.

1.4.3 Structure

This thesis is reported in four broad sections and eleven chapters. The first section of the thesis focuses on establishing the quality of current reporting of PROMs in LRRC, this is examined through a systematic review, which is reported in chapter 2. Following on from this, chapter 3 further examines the PROMs currently being used to report HrQoL in LRRC. This is undertaken through comparing outcomes in patients with PRC and LRRC utilising existing colorectal cancer registry data collected via the FACT-C measure.

The second section of the thesis focuses on the LRRC-QoL measure, recruitment to the cross-sectional cohort study completed in Australia in December 2019. The psychometric analysis of the LRRC-QoL in a combined UK and Australian cohort is reported in chapter 4. Chapter 5 describes the cross-cultural adaptation of the LRRC-QoL, to enable its use in several languages and cultures. Confirmation of the psychometric properties of the LRRC-QoL through external validation is reported in chapter 6. Recruitment of this

cohort of patients will also include assessment of HrQoL using the LRRC at 3, 6, and 12-months, and these outcomes are reported in chapter 7.

The third section of this thesis explores long-term survivorship in LRRC, chapter 8 describes a mixed-methods study to identify the survivorship issues which are relevant to patients who have undergone treatment for LRRC and remain disease-free for 3 years or longer.

The final section of this thesis comprises chapters 9 to 11, providing a discussion of this research and its findings. Chapter 9 focuses on the challenges associated with conducting research in LRRC on an international scale. The strategies employed to improve recruitment in this setting are outlined in chapter 10. Finally, chapter 11 summarises the overall findings and their implications.

Chapter 2 Systematic Review of Patient-Reported Outcome Measures in Locally Recurrent Rectal Cancer

2.1 Introduction

The surgical and oncological management of LRRC has evolved significantly since the turn of the millennium and clinical outcome reporting through single centre case series has been superseded by international, multi-centre collaboration to pool clinical data through networks such as the PelvEx collaborative (35). As clinical outcomes, including survival, continue to improve, researchers and clinicians have identified the need to focus on a more patient-centred approach to reporting outcomes in this group of patients (150). The inclusion of PROs in guiding shared decision-making is particularly important in the context of advanced malignancy such as LRRC. Increasingly radical surgical techniques, such as those described in chapter 1, including ELSiE and high sacrectomy, are generally accompanied by significant morbidity (66-68). In this context, balancing the patients' existing symptoms, the potential survival benefits to be gained from treatment and their impact on PROs such as overall QoL, physical function, sexual function, psychological and emotional well-being, is essential in enabling patients to make informed decisions regarding their care.

As the number of studies reporting PROs in LRRC steadily grows, it is crucial that those studies use suitable PROMs in order to produce valid and reliable results. The use of PROMs that are of poor quality or not validated for use in the target population of interest will lead to unreliable results. Additionally, the heterogeneity in the PROMs used and the timing of HrQoL assessment in LRRC means it is often impossible to compare HrQoL

outcomes across studies. There are existing guidelines and resources regarding the quality of PROMs and reporting of PRO data, these include the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) Risk of Bias checklist which was developed to assess risk of bias of studies on measurement properties of PROMS (151). This information regarding the quality of the individual studies is then used to determine the quality of the overall evidence on the measurement properties of a PROM (151). To date, there is no existing checklist available via the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network relating to the inclusion of PRO data for observational studies. The Consolidated Standards of Reporting Trials- Patient Reported Outcome (CONSORT-PRO) extension was developed to promote transparent reporting of trials including PROs as primary or secondary outcomes; facilitating the interpretation or PRO results for use in clinical practice (152).

The first chapter of this thesis details a number of issues relating to the existing body of literature regarding PROs in LRRC. The review reported in this chapter aims to build upon the evidence reported in previous reviews in this area (97, 103-105); with a particular focus on the methodological quality of the reporting of PROMs in LRRC, and an evaluation of the psychometric properties of PROMs currently being used in LRRC.

2.1.1 Objectives

- To identify the PROMs currently being used to report outcomes in patients with LRRC.
- To examine the methodological quality of studies reporting PROMs in LRRC, through:

- Evaluation of the quality of reporting of PROMs using criteria informed by the CONSORT-PRO extension (152, 153).
- Evaluation of the psychometric properties of PROMs used in LRRC against the COSMIN Risk of Bias checklist for PROMs, only PROMs which will satisfy the criteria for content validity will undergo full assessment, as per the checklist guidelines (151, 154).

2.2 Methods

This systematic review was conducted using a pre-specified protocol in keeping with Cochrane guidelines (155), and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist (156). The review was registered on the international prospective register of systematic reviews, PROSPERO (reference: CRD42022332577). A modified version of sections 2.2.1 – 2.3.5 originate from my paper "Systematic Review of Patient-Reported Outcome Measures in Locally Recurrent Rectal Cancer" published in Annals of Surgical Oncology (157).

2.2.1 Eligibility Criteria

Studies in adults (aged ≥ 18) with LRRC that included PROMs as a primary or secondary outcome measure were included. Studies in patients with LRRC undergoing any form of treatment, including surgery, chemotherapy, or radiotherapy, with curative or palliative intent, were eligible for inclusion. Studies in patients with a history of only local excision for PRC who developed a regrowth or recurrence were excluded. Only studies published in the English language were considered. Case reports, conference abstracts, study protocols, reviews and letters were excluded.

2.2.2 Information Sources

The search was undertaken using the Publisher Medline (PubMed), Excerpta Medica Database (EMBASE) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, including studies published from 1996 (PubMed), 1980 (EMBASE) and 1981 (CINAHL) up until 14th September 2022. The search strategy can be found in Appendix 1. Reference searching was also undertaken to identify additional studies. Studies describing the psychometric properties of the PROMs identified from this search were retrieved from citations and through manual searching to enable evaluation of the psychometric properties of the PROMs identified.

2.2.3 Selection Process

Titles and abstracts of studies retrieved were exported to EndNote X9 (Clarivate Analytics, Philadelphia, USA) and duplicates removed. The titles and abstracts were uploaded to Rayyan online software and screened for relevance by two authors (NM and ER). The full text for potentially eligible studies were retrieved and assessed, any queries regarding the eligibility of a study were resolved through discussion with senior authors.

2.2.4 Data Collection Process

Data pertaining to the characteristics of the studies included and the quality of the reporting of PROMs against criteria informed by the CONSORT-PRO checklist were extracted independently by authors NM and ER into Excel®. The COSMIN Risk of Bias checklist (151) was completed using the Excel® template available from the COSMIN website (158) independently by authors NM and FH. Any differences in ratings were discussed with senior authors to reach consensus.

2.2.5 Data Items

2.2.5.1 Characteristics of the Studies Included

The following characteristics were extracted for each study, including:

- Author,
- Year of publication,
- Country,
- Study design,
- Total number of patients in the study,
- Total number of patients with LRRC in the study,
- Number of patients in the study with PRO data,
- Inclusion of comparative group,
- Timing of PRO assessment,
- PROM(s) used,
- Citations given for PROM(s) used,
- Summary of study results,
- Reporting of the amount of PRO data collected at each time point,
- Approach to missing PRO data,
- Conclusions and discussion of the clinical relevance of PRO data.

2.2.5.2 Quality of Reporting of PROMs

There are currently no checklists available via the EQUATOR network regarding the inclusion of PRO data for observational studies. The CONSORT-PRO checklist was developed to promote transparent reporting of trials including PROs as primary or secondary outcomes; facilitating the interpretation or PRO results for use in clinical

practice (152). The CONSORT-PRO checklist was used to inform the evaluation of studies identified in relation to how the findings were reported and whether the methodology of the study and the PROMs used were sufficient to capture significant and meaningful findings.

2.2.5.3 Characteristics of PROMs Identified

The following characteristics were extracted for each PROM identified:

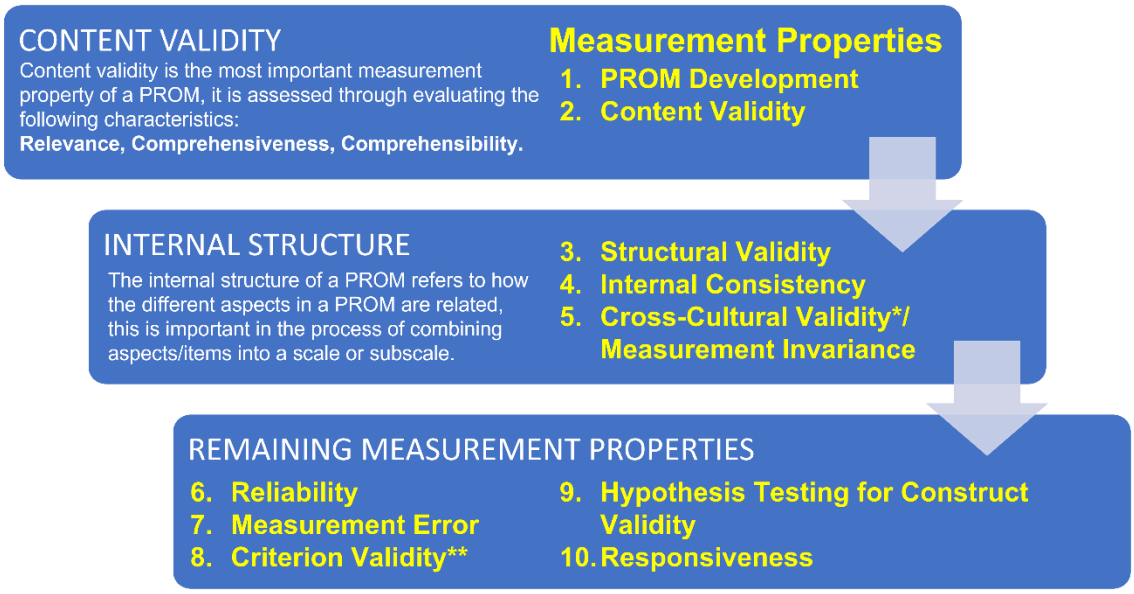
- Name of PROM,
- Patient-Reported Outcome being assessed,
- Disease-specific or generic PROM,
- Target population,
- Number of items,
- Scales in the PROM,
- Studies identified reporting PROM development.

2.2.5.4 PROM psychometric properties

The psychometric properties of the PROMs identified were evaluated using the COSMIN Risk of Bias checklist, which assesses risk of bias of studies on measurement properties of PROMs (151). Studies reporting the development or measurement properties of each PROM included were identified from references. The COSMIN Risk of Bias checklist was used to assess the quality of each study on the measurement property of each PROM; each item being rated as very good, adequate, doubtful, or inadequate. The overall quality of each study on a measurement property is determined by taking the lowest rating, "*worst score counts*" (159).

There are ten criteria in the COSMIN checklist, which are summarised in Figure 2.1. PROM development and content validity are the first to be assessed, if a PROM is deemed to have insufficient content validity, it should not undergo further assessment. Once sufficient evidence for content validity had been identified, the internal structure, meaning how the different aspects in a PROM are related, is assessed (95). This is important in the process of combining aspects/items into a scale or subscale (95). Following this, the remaining measurement properties are assessed. Studies are qualitatively summarised to give an overall rating of sufficient (+), insufficient (-), inconsistent (±), or indeterminate (?) for each measurement property (159). The quality of the evidence is also rated using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; high, moderate, low, or very low (160).

Figure 2.1: Summary of the COSMIN Risk of Bias Checklist



***Cross-cultural validity was not assessed in this review as the search strategy was not deemed suitable for identifying all studies describing cross-cultural adaptation of the measures included in this review.**

****The COSMIN panel determined that no gold standard exists for PROMs (161) and therefore criterion validity was not assessed in this review.**

2.2.6 Risk of Bias Assessment

Risk of bias was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (162), and the revised tool to assess Risk of Bias in randomised trials (RoB 2) (163), as advised in the Cochrane guideline (155).

2.2.7 Data Synthesis

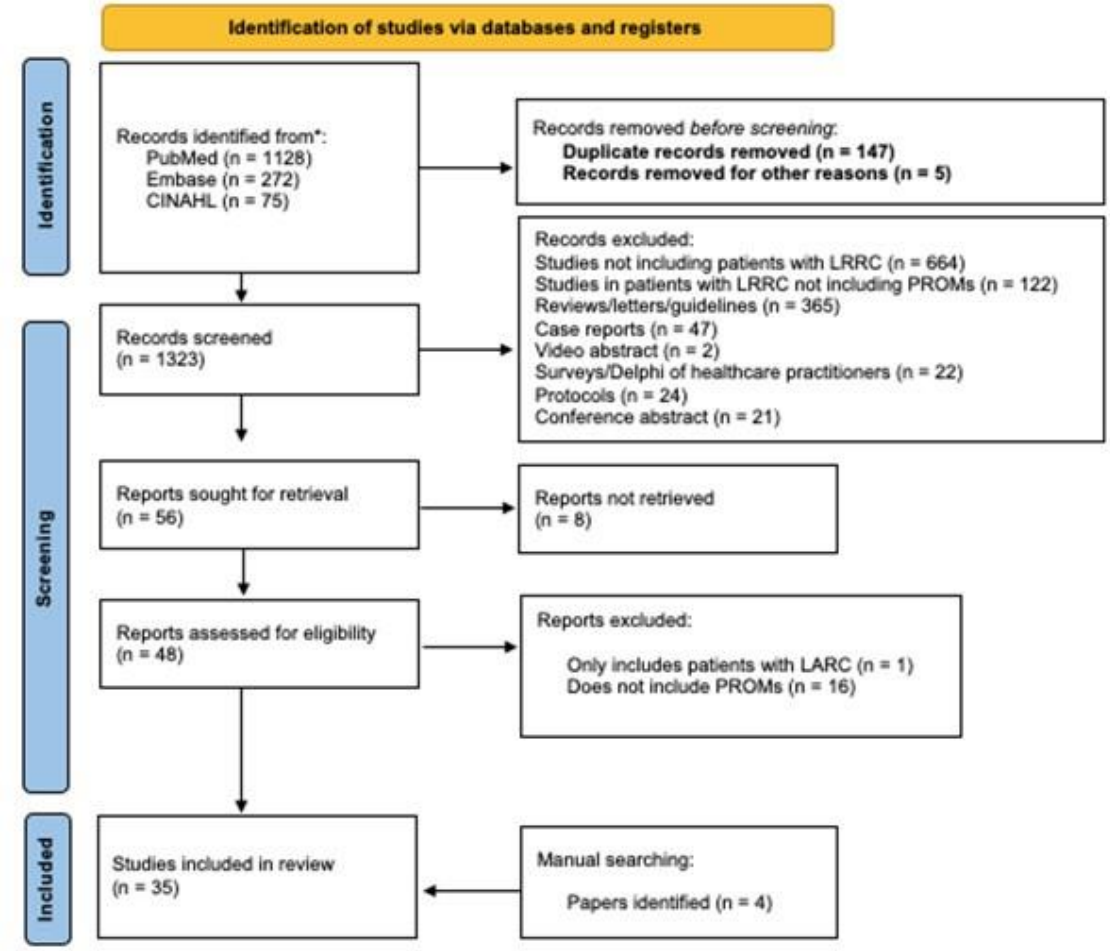
A basic descriptive analysis was undertaken to report the number of patients included in the studies identified and the proportion of patients with LRRC who contributed to assessments with PROMs. A descriptive analysis of compliance with criteria from the CONSORT-PRO and COSMIN Risk of Bias checklist was also reported. A quantitative synthesis was not planned as heterogeneity in the studies was anticipated.

2.3 Results

2.3.1 Study Selection

A total of 1475 references were identified using the search strategy described, there were 147 duplicates which were removed prior to screening and five studies were in animals. Abstracts were screened for 1323 references and the full text for 56 references were retrieved. Reasons for not including the retrieved records included an inability to access the full text and the studies not including PROMs. Thirty-one eligible references were included from the search strategy in addition to four references identified through manual searching, meaning 35 studies were included in the review (see Figure 2.2).

Figure 2.2: PRISMA flow diagram



2.3.2 Study Characteristics

A summary of the characteristics of the studies included in the review is presented in Table 2.1, including a total of 1914 patients with LRRC across all studies included, of which PROM data was reported for 1104 (57.7%) patients. Twenty-one (63.6%) of the studies identified were published in the last decade. The studies were conducted mostly in Europe (n=18, 51.4%), Australia (n=13, 37.1%) or the USA (n=4, 11.4%), with one study conducted in China (2.9%). Twenty-six (74.3%) studies recruited patients from a single centre. The majority were prospective cohort studies (n=19, 54.3%) in addition to

cross-sectional (n=7, 20.0%), case-control (n=5, 14.3%), retrospective cohort (n=2, 5.7%), and randomised studies (n=2, 5.7%). Nine (25.7%) of the studies identified included only patients with LRRC, in addition to two (5.7%) case control studies comparing patients with LRRC to other cohorts, with sample sizes of patients with LRRC ranging from 12 to 117 patients. The other 24 (68.6%) studies identified included combined cohorts of patients with primary and recurrent pelvic disease including LRRC, with sample sizes ranging from 12 to 710 patients in total. Median number of PROM assessments was two (IQR 1). In the 19 prospective, longitudinal studies identified, median follow-up was 12-months (IQR 15) the longest follow-up time point was 8 years (164).

Table 2.1: Summary of studies identified

	Country	Type of Study	Primary Outcome (s)	Total no patients	Patients included	Total no with LRRC	Total no with LRRC with PRO data	PROM data for LRRC	Inclusion of comparative group	Timing of PROM assessment	PROMs used
Huang 2022 (165)	Australia	Prospective cohort	QoL	271	PE 2008-2019	160	150	Yes	LARC vs LRRC	Baseline, 6, 12 months	FACT-C SF-36
Westerduin 2021 (166)	Netherlands, Belgium, and France	Cross-sectional	QoL	52	Redo anastomosis 2007-2017	2	2	No	Control group of 118 patients undergoing TME surgery for rectal cancer	Cross-sectional	LARS EORTC-C30 EORTC-CR29
Alahmadi 2021 (147)	Australia	Prospective cohort	QoL, Survival, Post-operative complications	710	PE 1994-2019	235	Not known	No	Elderly (>65) vs younger patients undergoing PE	Baseline, 6, 12, 18, 24, 30, 36, 48, 60 months	FACT-C SF-36
McCarthy 2020 (100)	Australia	Cross-sectional	QoL, lower limb motor, bowel, bladder, and sexual function	256	PE with sacrectomy 2008-2015	111	11	No	PE and sacrectomy vs PE only	Cross-sectional	SF-36 EORTC-C30 & CR29 MSTS LEFS SHIM FSFI
Van Ramshort 2020	Australia	Prospective cohort	Flap-related	87	PE with VRAM	30	Not known	No	PE with VRAM vs	Baseline, 6, 12, 18, 24 months	FACT-C SF-36

(167)			complications		reconstruction 2003-2016				PE no VRAM		
Denost 2020 (12)	France Australia	Prospective cohort	Surgical resection rate	154	LARC or LRRC 2015-2017	105	Not known	No	PE vs no PE	6, 12 months	SF-36 Distress thermometer Scale
Smith 2020 (168)	UK	Prospective cohort	Local control	30	SBRT for LRRC 2015-2019	30	30	Yes	No	Baseline 1, 3, 6 months, then 6 monthly intervals	EQ-5D EQ-VAS
Brown 2019 (28)	Australia	Prospective cohort	Survival, function, QoL	68	Sciatic and femoral nerve resection 1994-2018	33	Not known	No	Complete vs partial sciatic or femoral nerve resection	Baseline, 6, 12 months	FACT-C SF-36
Steffens 2018 (146)	Australia	Prospective cohort	Survival, QoL	515	PE 1994-2016 (PE 2008-2016 for QoL study)	181	119	No	No	Baseline, 6, 12, 18, 24, 30, 36, 48, 60 months	FACT-C SF-36
Lim 2018 (169)	Australia	Prospective cohort	Post-operative pain, pre-operative opiate use, post-operative pain	99	PE 2013-2014	51	42	Yes	No	Days 1, 2, 3 and 7	VNRS

Choy 2017 (98)	Australia	Prospective cohort	QoL	117	LRRC referred for PE 2008-2013	117	101	Yes	No	Baseline, 1, 3, 6, 9, 12 months	AQOL SF6D FACT-C
Quyn 2016 (101)	Australia	Prospective cohort	QoL, morbidity, survival	39	Palliative PE 1995-2015	30	Not known	No	No	Baseline, 1, 3, 6, 9, 12 months	AQOL SF-36
Cameron 2016 (170)	Norway	Prospective cohort	Severity of symptoms	51	Palliative pelvic radio-therapy 2009-2015	12	Not known	No	No	Baseline, completion of radiotherapy, 6, 12 weeks	EORTC-C30 BPI
Pellino 2015 (171)	Italy	Case-control	QoL	116	LRRC 2002-2011	45	40	Yes	Control group of patients with PRC and R0 resection	Baseline, 12, 36 months	EORTC-C30
Li 2015 (172)	China	Prospective cohort	Pain	31	LRRC 2009-2013	31	31	Yes	No	Baseline, 1 week, 1, 3, 6 months	VAS (pain)
Thaysen 2014 (173)	Denmark	Case-control	QoL	180	PE 2001-2008	62	62	No	Compared to population norms and a group undergoing standard rectal cancer surgery.	Baseline, 3, 6, 12, 18, 24 months	EORTC-C30 & CR38 SF-36
Beaton 2014 (174)	Australia	Cross-sectional	Morbidity, QoL	31	PE 1996-2007	17	17	No	Comparison of low,	Cross-sectional	FACT-C

									normal and high BMI		
Pusceddu 2013 (175)	Italy	Prospective cohort	Pain	12	LRRC with severe pain not responding to chemo-radiotherapy 2006-2010	12	12	Yes	No	Baseline, 1, 3, 6, 12, 22 months	VAS (pain)
Traa 2013 (176)	Netherlands	Prospective cohort	QoL, sexual function	439	LARC and LRRC 2000-2010	67	67	Yes	Population norms vs LARC vs LRRC	Cross-sectional	EORTC-C30 & CR38
Holman 2013 (177)	Netherlands	Cross-sectional	Flap-related complications, function following vaginal reconstruction, QoL	51	VRAM for LARC or LRRC 1994-2010	18	Not known	No	Patients with LARC and LRRC undergoing VRAM reconstruction vs patients not undergoing reconstruction.	Cross-sectional	EORTC-C30 & CR38
Brændengen 2011 (178)	Norway	Cross-sectional	Morbidity, sexual function	207	Non-resectable LARC or LRRC undergoing pre-op radiotherapy or chemorad	7	5	Yes	Patients receiving chemoradiotherapy vs those receiving radiotherapy	Cross-sectional	EORTC-C30 IIEF SVQ LENT SOMA St. Marks's FI score

					iotherapy 1996-2003						
Haapamaki 2011 (179)	Sweden	Cross-sectional	Physical function, QoL	19	Extralevator APER with gluteus maximus flap 2005-2007	1	1	No	No	Cross-sectional	EQ-5D EQ-VAS VAS
You 2011 (164)	USA	Prospective cohort	Survival, QoL, Pain	105	LRRC 1997-2007	105	54	Yes	Curative treatment surgery vs non-curative surgery and non-surgical treatment	Baseline, 3, 6, 9, 12, 24, 36, 60, 96 months	FACT-C BPI
Austin 2010 (180)	Australia	Case-control	QoL	44	PE 1996-2007	20	20	Yes	Patients undergoing PE vs patients with rectal cancer undergoing LAR or APER vs population norms	Cross-sectional	FACT-C SF-36
Zoucas 2010 (181)	Sweden	Prospective cohort	Morbidity, survival, QoL	85	PE 2003-2008	20	Not known	No	No	4, 16 months	EORTC-C30
Palmer 2008 (4)	Sweden	Case-control	QoL	142	LARC or LRRC 1991-2003	13	13	No	LARC and LRRC vs TME surgery	Cross-sectional	EORTC-C30 & CR38

									alone and population norms		
Miner 2003 (182)	USA	Prospective cohort	Morbidity, survival, QoL	105	LRRC 1997-1999	105	105	Yes	Palliative versus non-palliative treatment	Not specified	Not specified
Mannaerts 2002 (183)	Netherlands	Prospective cohort	Functional outcome	121	LARC or LRRC 1994-1999	66	39	Yes	LARC vs LRRC	6 months pre-treatment, median 14 months post-treatment	Questionnaire devised for the study including questions from the anal incontinence scale and MSKCC Sphincter Function Scale
Esanaola 2002 (184)	USA	Prospective cohort	Pain, QoL	45	LRRC 1999-2000	45	45	Yes	Non-operative palliation vs resection	Cross-sectional	FACT-C BPI
Camilleri-Brennan 2001 (185)	UK	Cross-sectional	QoL	75	LRRC 1992-1997	13	13	No	LRRC vs patients with PRC who did not develop recurrence	Cross-sectional	EORTC-C30 & CR38
Mannaerts 2001 (186)	Netherlands	Retrospective cohort	Urological function	121	LARC or LRRC 1994-1999	66	39	Yes	LARC vs LRRC	Cross-sectional	Not specified
Guren 2001 (187)	Norway	Case-control	QoL	37	Patients undergoing urinary diversion for LARC	12	12	No	Patients undergoing urinary diversion vs patients	Cross-sectional	EORTC-C30 & CR38 & BLM30 (6 items only)

					or LRRC since 1991				who did not undergo urinary diversion vs population norms		
Trotter 1996 (188)	Australia	Randomised study	Disease progression, toxicity, QoL	73	LRRC or primary inoperable rectal cancer 1985-1991	64	64	No	Microwave therapy combined with external beam radiotherapy vs standard external beam radiotherapy	Weekly during treatment and then every 4 weeks	Spitzer
Scheithauer 1993 (189)	Austria	Randomised study	Survival, QoL	36	Inoperable metastatic or recurrent colorectal cancer 1988-1989	Not known	Not known	No	Patients receiving chemotherapy vs best supportive care vs healthy volunteers	Baseline, every 2 months	FLIC
Wanebo 1987 (190)	USA	Retrospective cohort	Morbidity, mortality, survival, QoL	28	LRRC	28	10	Yes	No	Cross-sectional	Not specified

Abbreviations: QoL – quality of life, PROM – patient-reported outcome measure, PE - pelvic exenteration, LRRC – locally recurrent rectal cancer, LARC – locally advanced rectal cancer, FACT-C - Functional Assessment of Cancer Therapy – Colorectal Measure, SF-36 – 36-Item Short Form Survey, TME – total mesorectal excision, LARS – Low Anterior Resection Syndrome score, EORTC-C30 – European Organisation for Research and Treatment of Cancer Core Measure, EORTC-CR29/CR38 – European Organisation for Research and Treatment of Cancer Colorectal Module, MSTS – Musculoskeletal Tumour Society Score, LEFS – Lower Extremity Functional Scale, SHIM – Sexual Health Inventory for Men, FSFI – Female Sexual Function Index, VRAM - Vertical Rectus Abdominis Myocutaneous flap, SBRT – Stereotactic Body Radiotherapy, EQ-5D – EuroQoL measure of health-related quality of life, EQ-VAS – EuroQoL Visual Analogue Scale, VNRS – Verbal Numerical Rating Scale, SF6D – Short Form Six-Dimension, AQOL – Assessment of Quality of Life, BPI – Brief Pain Inventory, R0 – Complete Surgical Resection, VAS – Visual Analogue Scale, BMI – Body Mass Index, IIEF – International Index of Erectile Function, SVQ – Sexual function – Vaginal changes Questionnaire, LENT-SOMA – Late Effects of Normal Tissue – Subjective , Objective, Management and Analytic, St. Mark's FI Score – St. Mark's Faecal Incontinence Score, APER – Abdominoperineal Excision of the Rectum, LAR – Low Anterior Resection, MSKCC – Memorial Sloan Kettering Cancer Center, EORTC-BLM30 – European Organisation for Research and Treatment of Cancer Muscle Invasive Bladder Cancer Measure, PRC – Primary Rectal Cancer, FLIC – Functional Living Index – Cancer.

2.3.3 Risk of Bias

Risk of bias was high overall, with 32 (91.4%) studies highly or seriously biased (see figures 3 and 4). The domains which demonstrated the highest degree of bias for observational studies were confounding, participant selection, and missing data. The domains which demonstrated the highest degree of bias for randomised studies were missing outcome data and selection of the reported result.

Figure 2.3: ROBINS-I risk of bias for observational studies

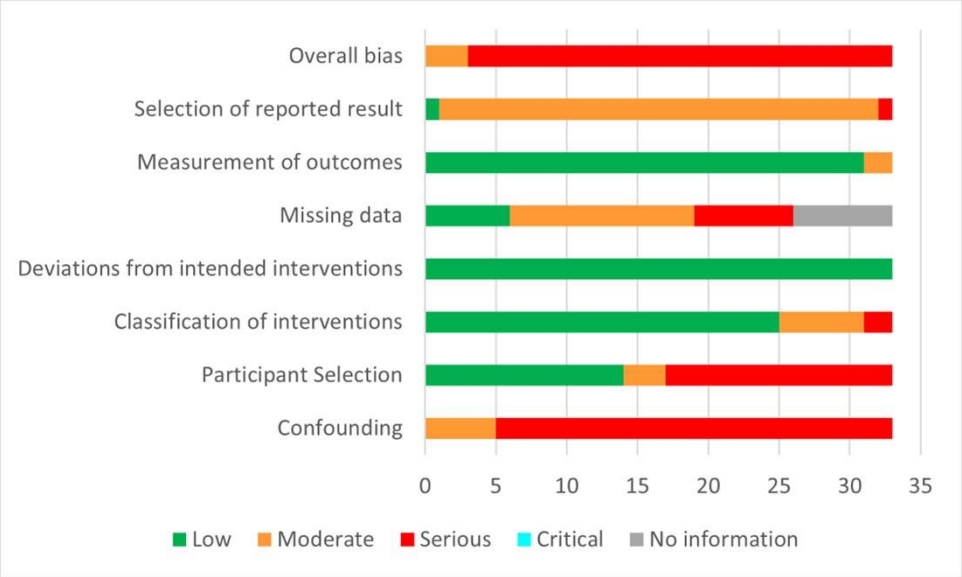
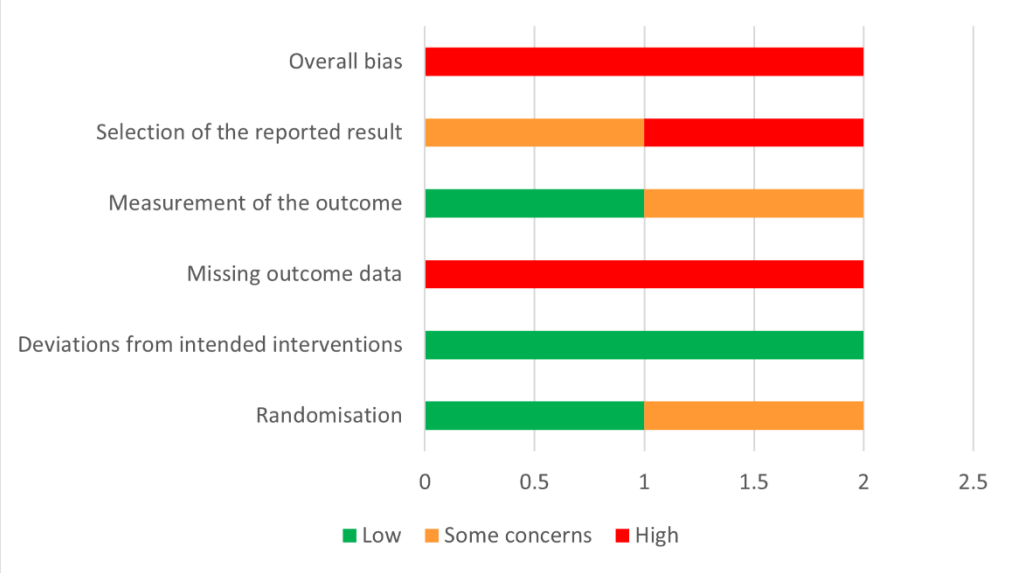


Figure 2.4: RoB 2 risk of bias for randomised studies

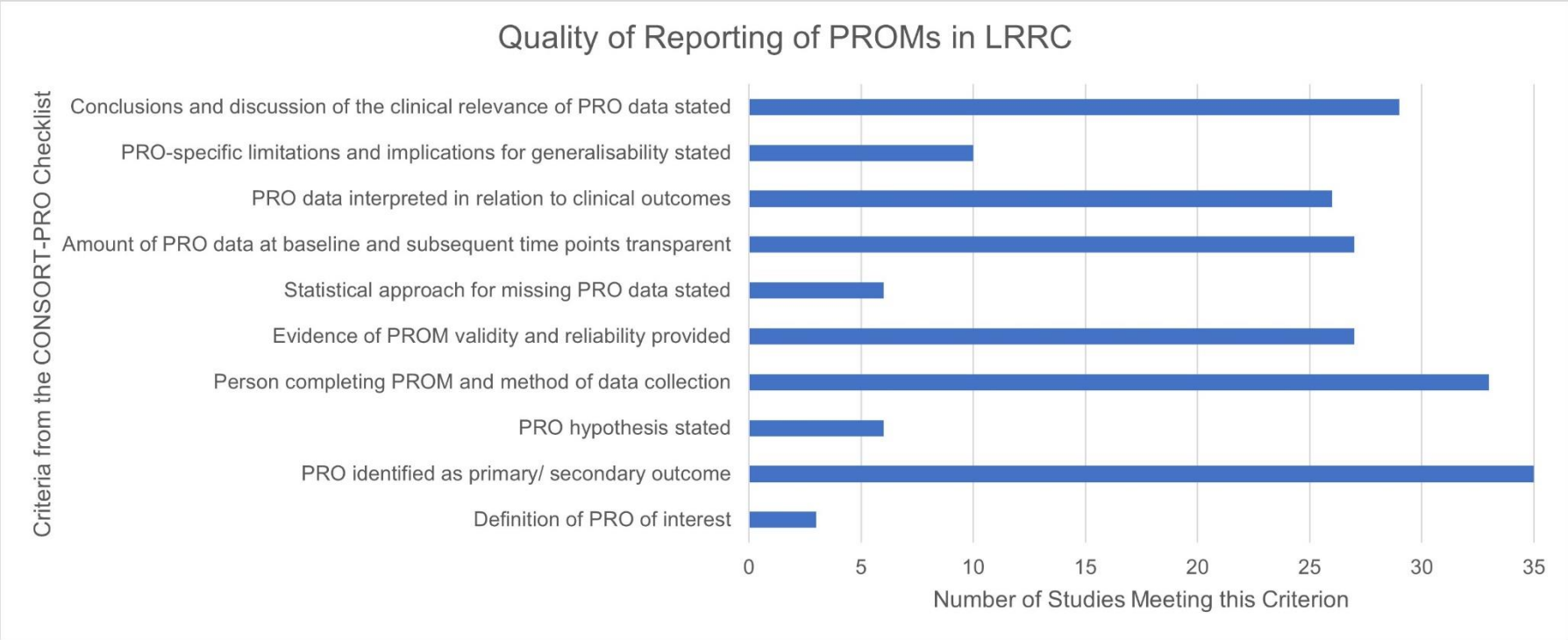


2.3.4 Results of Individual Studies

2.3.4.1 Quality of Reporting of PROMs

The assessment of the studies identified against criteria informed by the CONSORT-PRO checklist are illustrated in Figure 2.5. None of the studies included in the review met all eleven criteria for the quality of reporting of PROMs, with an overall median score of 5.8 (58.3%) criteria. The least reported criteria were defining the PROM of interest (n=3, 8.6%), describing the statistical approach to missing PRO data (n=6, 17.1%), and detailing a PRO hypothesis (n=6, 17.1%). The most commonly met criterion was the identification of a PRO as a primary or secondary outcome (n=35, 100.0%).

Figure 2.5: Quality of reporting of PROMs in LRRC



2.3.4.2 Characteristics of the PROMs Identified

Seventeen PROMs and two clinician-reported outcome measures (Musculoskeletal Tumour Society Score (MSTS) and Spitzer) were identified. The most commonly reported PROMs were the EORTC QLQ-C30 (n=12, 34.3%)(4, 100, 166, 170, 171, 173, 176-178, 181, 185, 187), the SF-36 (n=11, 31.4%)(12, 28, 98, 100, 101, 146, 147, 165, 167, 173, 180), the FACT-C (n=10, 28.6%)(28, 98, 146, 147, 164, 165, 167, 174, 180, 184), and the EORTC QLQ-CR29 (n=2, 5.7%)(100, 166) when combined with its predecessor, the EORTC QLQ-CR38 (n=6, 17.1%) (4, 173, 176, 177, 185, 187).

Four of the PROMs identified were specific to patients with cancer (see Table 2.2), however, there were no disease-specific PROMs for patients with LRRC. The cancer-specific measures included the EORTC QLQ-C30 which is a measure of QoL in patients with cancer and the Functional Living Index – Cancer (FLIC) is a measure of functional state in adult patients with cancer. Two measures which are cancer-site specific were also identified; the EORTC QLQ-CR29 (formerly the EORTC QLQ-CR38) and FACT-C which are both measures of QoL in patients with primary colorectal cancer.

Table 2.2: Summary of cancer-specific measures identified

Measure	Patient-Reported Outcome	Target Population	No of Items	Scales	No of Languages/ Dialogues	Total no of studies identified using this PROM	Studies identified using this PROM
European Organisation for Research and Treatment of Cancer Core Measure (EORTC QLQ-C30)	QoL	Patients with cancer	30	Functional scales: - Physical - Role - Cognitive - Emotional - Social	117 (191)	12	(4, 100, 166, 170, 171, 173, 176-178, 181, 185, 187)

				Symptom scales: - Fatigue - Pain - Nausea and vomiting Global health status			
Functional Living Index – Cancer (FLIC)	Functional state	Patients with cancer	22	Psychological Physical Symptoms Family Social	15 (192)	1	(189)
European Organisation for Research and Treatment of Cancer Colorectal Module (EORTC QLQ-CR29)	QoL	Patients with primary colorectal cancer	29	Urinary frequency Blood or mucus in stools Stool frequency Body image	66 (193)	2	(100, 166)
European Organisation for Research and Treatment of Cancer Colorectal Module (EORTC QLQ-CR38)	QoL	Patients with primary colorectal cancer	38	Body image Sexuality Micturition problems Gastrointestinal symptoms Chemotherapy side-effects Problems with defaecation Stoma-related problems Male and female sexual problems	10 (194)	6	(4, 173, 176, 177, 185, 187)
Functional Assessment of Cancer Therapy – Colorectal Measure (FACT-C)	QoL	Patients with primary colorectal cancer	36	Emotional Well-Being Social Well-Being Functional Well-Being Physical Well-Being	40 (195)	10	(28, 98, 146, 147, 164, 165, 167, 174, 180, 184)

				Colorectal Cancer Subscale			

Seven PROMs which relate to forms of function or functional limitations were identified (Table 2.3), including bowel function, physical function, and sexual function. The Low Anterior Resection Syndrome (LARS) score is a measure to assess bowel dysfunction following low anterior resection for rectal cancer and the St. Mark's Faecal Incontinence Score for adult patients with faecal incontinence. The Lower Extremity Functional Scale (LEFS) is a measure of lower extremity physical function designed for patients with lower extremity orthopaedic conditions. Four of the measures identified were measures of sexual function, including the Sexual Health Inventory for Men (SHIM) and the International Index of Erectile Function (IIEF) which are measures of erectile dysfunction developed for use in male patients with a history of erectile dysfunction and the Female Sexual Function Index (FSFI) measure of sexual function for female patients with a history of sexual arousal disorder and the Sexual function – Vaginal changes Questionnaire (SVQ) measure of sexual and vaginal problems developed for patients with a history of gynaecological cancer.

Table 2.3: Summary of measures related to function

Measure	**Patient-Reported Outcome**	**Target Population**	**No of Items**	**Scales**	**No of Languages / Dialogues**	**Total no of studies identified using this PROM**	**Studies identified using this PROM**
Low Anterior Resection Syndrome (LARS) score	Low Anterior Resection Syndrome	Patients who have undergone low anterior resection for rectal cancer	5	N/A	24 (196)	1	(166)
Lower Extremity	Lower extremity	Patients with lower extremity	20	N/A	14 (192)	1	(100)

Functional Scale (LEFS)	physical function	orthopaedic conditions					
Sexual Health Inventory for Men (SHIM)	Erectile dysfunction	Male patients with erectile dysfunction	5	N/A	9 (192)	1	(100)
International Index of Erectile Function (IIEF)	Erectile dysfunction	Male patients with erectile dysfunction	15	Erectile function Orgasmic function Sexual desire Intercourse satisfaction Overall satisfaction	88 (192)	1	(178)
Female Sexual Function Index (FSFI)	Sexual function	Female patients with sexual arousal disorder	19	Desire Arousal Lubrication Orgasm Satisfaction Pain	52 (192)	1	(100)
Sexual function – Vaginal changes Questionnaire (SVQ)	Sexual and vaginal problems	Gynaecological cancer patients	20 core items (7 additional items for use in follow-up)	Intimacy Sexual interest Global sexual satisfaction Vaginal changes Sexual functioning	Not known	1	(178)
St. Mark's Faecal Incontinence Score	Faecal incontinence	Adult patients with faecal incontinence	7	N/A	Not known	1	(178)

Six of the PROMs identified were generic measures (see Table 2.4), including three measures of QoL for use in adult patients; the 36-Item Short Form Survey (SF-36), EuroQoL (EQ-5D), and Assessment of Quality of Life (AQOL-4D), two measure of pain

intensity; the Verbal Numerical Rating Scale (VNRS) and Visual Analogue Scale (VAS), and finally one measure of pain, the Brief Pain Inventory (BPI).

Table 2.4: Summary of generic measures identified

Measure	Patient-Reported Outcome	Target Population	No of Items	Scales	No of Languages/ Dialogues	Total no of studies identified using this PROM	Studies identified using this PROM
36-Item Short Form Survey (SF-36) including the Short Form Six-Dimension (SF6D)	QoL	Adult patients	36	Energy/vitality Physical functioning Bodily pain General health perceptions Physical role functioning Emotional role functioning Social role functioning Mental health	2 available via RAND (197), 191 listed on ePROVIDE (192)	11	(12, 28, 98, 100, 101, 146, 147, 166, 167, 173, 180)
EuroQoL (EQ-5D) including the Visual Analogue Scale (EQ-VAS)	QoL	Adult patients	5	Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	183 (198)	2	(168, 179)
Verbal Numerical Rating Scale (VNRS)	Pain Intensity	Adult patients	10-point scale	N/A	Not known	1	(169)
Visual Analogue Scale (VAS)	Pain Intensity	Adult patients	100mm line	N/A	Not known	3	(172, 175, 179)
Assessment of Quality of Life (AQOL-4D)	QoL	Adult patients	15	Illness Independent living Social relationships Physical senses	7 (199)	2	(98, 101)

				Psychological wellbeing			
Brief Pain Inventory (BPI)	Pain	Adult patients	11	Pain intensity Pain interference	53 (200)	3	(164, 170, 184)

The three remaining measures included (see Table 2.5), were not patient-reported but clinician-reported. Those included the Late Effects of Normal Tissue – Subjective, Objective, Management, and Analytic (LENT-SOMA) scoring system for late effects of radiotherapy, including a subjective scale to be completed by patients with the remainder being completed by clinicians. The Spitzer is a clinician-reported measure of QoL for patients with cancer or other chronic diseases and the Musculoskeletal Tumour Society Score (MSTS) is a clinician-reported measure of physical function for patients with musculoskeletal neoplasms.

Table 2.5: Summary of other measures identified

Measure	**Patient-Reported Outcome**	**Target Population**	**No of Items**	**Scales**	**No of Languages / Dialogues**	**Total no of studies identified using this PROM**	**Studies identified using this PROM**
Late Effects of Normal Tissue – Subjective, Objective, Management, and Analytic (LENT-SOMA) scales	Late effects of radiotherapy	Adult patients who have received radiotherapy	5 (for subjective rectum scale)	Tenesmus Mucosal loss Sphincter control Stool frequency Pain	Not known	1	(178)
Spitzer *designed to be used as a clinician-	QoL	Patients with cancer or other chronic diseases	5	Activity Daily life Health perceptions Social support	5 (192)	1	(188)

reported outcome measure				Behaviour			
Musculos keletal Tumour Society Score (MSTS) *designed to be used as a clinician-reported outcome measure	Physical function	Patients with musculos keletal neoplasms	6	Pain Function Emotional acceptance Criteria specific to the lower extremity: - Use of supports - Walking - Gait Criteria specific to the upper extremity: - Hand positioning - Manual dexterity - Lifting ability	Not known	1	(100)

2.3.5 PROM Psychometric Properties

The psychometric properties were only assessed for PROMs and not the LENT-SOMA or the clinician-reported outcome measures, Spitzer and MSTS. The psychometric properties of the EORTC QLQ-CR38 were also not assessed given this module has been superseded by the EORTC QLQ-CR29. A summary of the overall ratings and grading of quality of evidence for the measurement properties of the five PROMs which underwent full COSMIN review is included in Table 2.6. All other PROMs did not meet criteria for content validity. Content validity is the most important measurement property of a PROM and therefore full review is not advised if a PROM does not meet criteria for content validity. Cross-cultural validity, measurement invariance measurement error and criterion validity were not assessed.

2.3.5.1 Content validity

None of the PROMs identified were developed specifically for patients with LRRC (see Tables 2.2-2.5) and no studies were identified in which the psychometric properties of these PROMs were evaluated in patients with LRRC. A pragmatic decision was therefore undertaken to assess content validity in relation to the specific group in which the PROM had been developed to gain an understanding of the overall quality of the PROMs being used in LRRC. Content validity was deemed adequate for five PROMs, when assessed in the context of the specific subset of patients for which they had been developed. All other PROMs did not meet the criteria for content validity.

The PROMs which did meet the criteria for content validity included the FACT-C, which was developed as a measure of QoL in patients with primary colorectal cancer (201), the EORTC QLQ-C30, which was developed as a measure of QoL in patients with cancer and was initially developed in a cohort of patients with lung cancer (202), the EORTC QLQ-CR29, which was developed as a measure of QoL in patients with primary colorectal cancer (109), the EQ-5D-5L which was developed as a generic measure of QoL through focus groups including healthy participants and those with chronic disease (203), finally the SF-36, which was developed as a generic measure of QoL in patients with chronic conditions and was initially developed in a cohort of patients with diabetes, hypertension, heart disease and/or depression (204, 205). All five PROMs demonstrated moderate to high quality evidence for the three aspects of content validity assessed: relevance, comprehensiveness, and comprehensibility. However, it is worth noting that reporting of assessment for comprehensiveness could generally be improved by describing the methods undertaken more explicitly.

In terms of the PROMs which did not meet the COSMIN criteria for content validity, these were predominately disease-specific measures. The Sexual Health Inventory for Men (SHIM) is an abridged version of the International Index of Erectile Function (IIEF). The IIEF development included interviews with patients with erectile dysfunction and their partners, the IIEF did not meet the COSMIN criteria for content validity due to assessment of relevance, comprehensibility, and comprehensiveness not being described in sufficient detail (206). The Sexual function – Vaginal changes Questionnaire (SVQ) development included interviews with patients with gynaecological cancer, it was given an inconsistent rating for relevance, an insufficient rating for comprehensiveness and a sufficient rating for comprehensibility (207). The Female Sexual Function Index (FSFI) was developed for patients with female sexual arousal disorder and its development included interviews with this group of patients in addition to female volunteers from the general population, the measure was given an inconsistent rating for relevance and insufficient ratings for both comprehensiveness and comprehensibility (208).

The Lower Extremity Functional Scale (LEFS) involved patients with a history of lower-extremity musculoskeletal dysfunction (defined as any condition of the joints, muscles, or other soft tissues) in the process of item development, however there was no evidence that its relevance, comprehensiveness, and comprehensibility have been established in the population of interest and it was therefore rated as insufficient for content validity (209). The St. Mark's Faecal Incontinence Score did not meet the criteria for relevance, comprehensibility, or comprehensiveness due to not involving patients with faecal incontinence, who were the population of interest, in the development process (210). The Low Anterior Resection Syndrome (LARS) score was developed to assess bowel dysfunction in patients who had undergone low anterior resection for rectal cancer, the

LARS score demonstrated good evidence for comprehensibility and comprehensiveness. However, it was rated inconsistent in relation to the criteria for relevance, due to insufficient involvement of patients in the initial process of item generation (211). The Functional Living Index – Cancer (FLIC) development involved interviews with patients, though the characteristics of these patients were not described, this was followed by review of the items by a panel which included one male and one female patient and two patient spouses (212). Ultimately it was rated as inconsistent for relevance and insufficient for both comprehensiveness and comprehensibility.

In terms of the generic measures identified, the psychometric properties of the Assessment of Quality of Life (AQoL-4D) were assessed as this is the version referenced (213), this measure was developed through interviews with a range of medical conditions. The AQoL-4D did not meet the COSMIN criteria for content validity particularly due to a lack of evidence demonstrating comprehensiveness or comprehensibility, however newer versions have since been developed and validated (214). It was not possible to evaluate the content validity of the Visual Analogue Scale (VAS) or Verbal Numerical Rating Scale (VNRS) given the nature of these single-item measures of pain intensity, in addition, the VAS has been in use for a century (215). It was also not possible to evaluate the BPI fully due to being unable to retrieve the full text for the PROM development study (216), ratings were therefore determined from the development of the first version of the BPI, namely the Wisconsin Brief Pain Questionnaire (217) and did not meet criteria for content validity due to lack of sufficient evidence.

2.3.5.2 Internal Structure and Remaining Measurement Properties

Content validity is the most important measurement property of a PROM and therefore full review is not advised if a PROM does not meet criteria for content validity. A summary of the findings for the internal structure and remaining measurement properties of the five PROMs which were deemed to meet the criteria for content validity can be found in Table 2.6.

Table 2.6: Quality of the evidence for the measurement properties of the PROMs – FACT-C, EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and SF-36

	FACT-C		EORTC QLQ-C30		EORTC QLQ-CR29		EQ-5D-5L		SF-36	
	Overall rating	**Quality of Evidence**	**Overall rating**	**Quality of Evidence**	**Overall rating**	**Quality of Evidence**	**Overall rating**	**Quality of Evidence**	**Overall rating**	**Quality of Evidence**
	+ / - / ?	**High, moderate, low, very low.**	**+ / - / ?**	**High, moderate, low, very low.**	**+ / - / ?**	**High, moderate, low, very low.**	**+ / - / ?**	**High, moderate, low, very low.**	**+ / - / ?**	**High, moderate, low, very low.**
Content validity	+	Moderate	+	High	+	High	+	High	+	High
Relevance	+	High	+	High	+	High	+	High	+	High
Comprehensiveness	+	Moderate	+	High	+	High	+	High	+	High
Comprehensibility	+	Moderate	+	High	+	High	+	High	+	High
Structural validity	+	High	+	High	+	High	+	High	+	High
Internal consistency	+	High	+	High	+	High	N/A	N/A	+	High
Reliability	+	High	?	Moderate	+	High	?	Moderate	?	Moderate
Construct validity	+	High	+	Moderate	+	High	+	High	+	Moderate
Responsiveness	?	Low	?	Moderate	?	Moderate	?	Low	+	High

2.4 Discussion

The central finding of this review is the ongoing lack of validated measures for use in patients with LRRC, despite the evidence of an increased focus on reporting PROs in this cohort of patients. The majority of studies (n=21, 63.6%) having been reported during the last decade. This systematic review did not identify a disease-specific PROM available for use in LRRC and none of the PROMs identified met the COSMIN criteria for content validity in the context of LRRC. The most used PROMS in LRRC were the FACT-C (n=10, 28.6%), SF-36 (n=11, 31.4%) EORTC QLQ-C30 (n=12, 34.3%) and CR29 (n=8, 22.9%), none of which have demonstrated content validity specifically for patients with LRRC.

Overall, the findings build on the existing evidence (97, 103-105) of variable methodological quality of reporting of PROMs within small sample sizes and mixed disease cohorts. This review focuses specifically on the methodological quality of PRO reporting using criteria informed by the CONSORT-PRO checklist; common weaknesses were identified in several domains, including defining the PRO of interest, describing the statistical approach to missing data and stating PRO-specific limitations and implications for generalisability. These results were comparable to those reported in Efficace et al.'s pooled analysis of randomised cancer trials utilising CONSORT-PRO (218), though methods of PRO data collection had higher levels of reporting in this current review. Ultimately, the key limitation identified is the lack of input from patients with LRRC in the PROMs currently being used, with none demonstrating content validity for use in this context. Content validity is the most important measurement property of a PROM; for PROMs to give meaningful results in LRRC, it is essential that they are relevant to

patients with LRRC and present a comprehensive assessment of the construct of interest. Without addressing the lack of an appropriate PROM for use in patients with LRRC, the impact of addressing issues such as heterogeneity in the groups of patients included, the comparator groups used, and the timing of PROM assessment, is likely to be limited.

The lack of content validity demonstrated both in relation to patients with LRRC and in the context of the specific groups of patients in which the PROMs identified were developed, could be summarised largely into two categories. The first being that some of the PROMs identified did not involve patients in their development process or did so minimally, which is inadequate. Secondly, the processes involved in establishing content validity, which typically involve interviews or focus groups with patients experiencing the condition of interest, were poorly described. It is possible that this process may have been performed sufficiently but was not described in sufficient detail in resultant publications and was therefore deemed inadequate. The poor reporting of content validity could relate to limitations on word counts in publishing and authors choosing to focus on the statistical psychometric evaluation of a PROM's measurement properties. Additionally, many of the PROMs identified were developed prior to the publication of the COSMIN guidelines and perhaps a degree of leniency should be granted when assessing PROMs against criteria published more recently. The development of a PROM is a rigorous process requiring an in depth understanding of methodology including qualitative research methods and psychometric analysis. The term "validated" is commonly employed to describe PROMs utilised within research studies, including those in patients with LRRC, and can be misleading when clarity is not provided regarding the authors' intended meaning. It is important that authors explicitly state the specific group of patients in which PROMs have been "validated"; as PROMs can only be considered to convey robust and meaningful results when they are used in groups of patients for which

they have been shown to have content validity. The increasing interest in utilising PROMs and reporting PROs in LRRC is to be commended, however, it is important that researchers carefully consider the constructs they choose to measure and the tools they select for this purpose to ensure that their results are accurate and relevant to patients with LRRC. Increasing awareness of the psychometric properties of existing PROMs and the rigorous development processes required to ensure high-quality PROMs are produced, is an important factor in improving the quality of reporting of PROs in LRRC.

The LRRC-QoL conceptual framework was developed through undertaking a systematic review and qualitative focus groups to identify the HrQoL issues relevant to patients with LRRC (104, 106). The themes identified were symptoms, sexual function, psychological impact, role and social functioning, future perspective and healthcare service utilisation and delivery. Nineteen (54.3%) of the studies identified in this review have been published since this work (12, 28, 98, 100, 101, 146, 147, 167-176), using a median of two PROMS, with the EORTC QLQ-CR29 and FACT-C most used. The EORTC QLQ-CR29 and FACT-C have also both demonstrated robust psychometric properties, including content validity, in patients with primary colorectal cancer (201, 219). When compared with the LRRC-QoL conceptual framework (106), the EORTC QLQ-CR29 covers 50% of the LRRC-specific domains, including symptoms, sexual function, and psychological impact. It does not however cover the domains of role functioning, or future perspective. The FACT-C covers 66.6% of the LRRC-specific domains identified in the LRRC-QoL conceptual framework including symptoms, psychological impact, role functioning, and future perspective, it does not cover sexual function. Neither the EORTC QLQ-CR29 or FACT-C cover issues relating to healthcare services, self-efficacy and body image, future plans, disease re-recurrence, gynaecological or locomotor symptoms. The evidence identified reporting outcomes utilising these PROMs should not be

completely disregarded, as the EORTC QLQ-CR29 and FACT-C capture a proportion of the issues relevant to patients with LRRC. However, it should be interpreted with caution, as they are unlikely to capture the full scope and complexity of the range of issues patients with LRRC experience (104, 106).

A number of PROMs which measure issues relevant to patients with LRRC were identified in this review; urinary and sexual function were evaluated using specific questionnaires for this purpose by two studies (100, 178), however, other questionnaires, such as the EORTC QLQ-CR29, also contain items regarding sexual and urinary function. No specific PROMs regarding stoma-related quality of life were used in the studies identified, despite being relevant to patients with LRRC (106). However, PROMs such as the EORTC QLQ-CR29 and FACT-C contain items specifically for patients with stomas. The increasing number of PROMs currently being used in LRRC reflects the lack of an existing disease-specific measure which adequately reports all the PROs relevant to this cohort of patients. The trend to include several PROMs is likely to reflect the greater understanding of the wider issues which affect patients with LRRC. However, the measures identified in this review are not valid for use in patients with LRRC and therefore this is not a psychometrically robust approach to addressing the lack of a LRRC disease-specific measure. Additionally, this approach potentially increases the burden of participation for patients, without sufficient methodological justification.

There are limitations related to the evidence included in this review, notably, most of the studies identified have a high risk of bias (n=32, 91.4%) and their findings should generally be interpreted with caution. They also present a predominately Western perspective of PROs in LRRC and demonstrate a lack of multi-centre, international

reporting of PROs in LRRC. Furthermore, 13 (37.1%) of the studies identified were conducted within a single centre, reporting cohorts of patients which may potentially overlap.

The CONSORT-PRO checklist was adapted for use in this review and though it has widely been used to assess quality of reporting, it is worth noting that it was not designed to be used for this purpose (152, 220). In developing the search strategy for this review, we trialled using the COSMIN-recommended search strategy to identify studies validating PROMs for use in LRRC, however, no relevant studies were identified via this method. The final search strategy required manually searching references to identify studies describing the psychometric properties of the PROMs included, as such, it is possible that not all relevant studies were identified which may have led to reporting bias and could affect the COSMIN ratings given for the PROMs. For this reason, it was not possible to assess the availability and quality of translated PROMs in this review. To further the success of initiatives such as the PelvEx collaborative in advancing international outcome reporting in this cohort of patients (35) and integrating PRO data, it is essential that PROMs undergo a rigorous process of cross-cultural adaption.

This review highlights several key areas for improvement in the reporting of PROs in LRRC, these include giving a definition of the PRO of interest and adequately describing and utilising a recognised statistical approach for handling missing PRO data. Future studies should also focus on reporting international, multi-centre outcomes, to ensure that results are more generalisable internationally. The lack of an EQUATOR network checklist specifically for the inclusion of PRO data in observational studies was also

highlighted as potential area for future work which would be useful for researchers in improving the quality of their reporting.

There are several approaches which could be employed to address the lack of PROMs with content validity for patients with LRRC. It is possible to demonstrate the content validity of existing PROMS specifically for LRRC, however, given the narrow breadth of relevant HrQoL issues captured by existing measures, this approach will require significant revision to make these measures applicable to LRRC (106). Employing a modular approach to PROM assessment in LRRC is an alternative approach, provided both the core cancer and site-specific measures are appropriately revised and validated for use in LRRC. Development of a new disease-specific PROM for use in patients with LRRC, to capture concerns that are specific to patients with LRRC which can be used to more accurately monitor the impact of particular treatments on PROs such as HrQoL, therefore represents the most realistic and valid approach (221). As outlined in chapter 1, this thesis describes the external validation and cross-cultural adaptation of the LRRC-QoL PROM; the first disease-specific measure developed to assess HrQoL in LRRC (108). Cross-cultural adaptation will produce versions of the LRRC-QoL for use in several countries, including low and middle-income countries which have previously been underrepresented in the reporting of PROs in LRRC. The LRRC-QoL has also been designed to be used in combination with EORTC QLQ-C30, in a modular fashion, which would allow comparison across patient groups.

2.5 Conclusion

This systematic review highlights key methodological issues in the current state of reporting of PROs in LRRC, finding that none of the PROMs currently being used in LRRC are able to provide meaningful results within this context. Future studies in this disease area should focus on utilising PROMs that have undergone a robust development process with the inclusion of patients with LRRC, to ensure high quality, accurate results which are relevant to this patient group. The development of a disease-specific PROM for patients with LRRC or undertaking content validity studies of existing PROMs are approaches which could be employed to enable this, in addition to undertaking cross-cultural adaptation to enable international reporting of outcomes. Greater emphasis should also be placed on the way in which PROMs data are reported and analysed, particularly in defining the PRO of interest and in handling missing PROM data, to ensure that results are reliable. The results of this review support the intention to cross-culturally adapt and validate the LRRC-QoL for use on an international platform, with a view to improving the quality of PRO data in this cohort of patients and is described in further detail in this thesis.

Chapter 3 A Registry-Based Study Comparing Health-Related Quality of Life Outcomes in patients with Primary Rectal Cancer and Locally Recurrent Rectal Cancer

3.1 Introduction

National clinical registries of routinely collected healthcare data and linkage of such datasets, present several benefits and potential applications. These include providing information regarding the incidence of specific conditions and their clinical characteristics, identifying variation both in healthcare delivery and clinical outcomes, and utilising this data to inform interventions and improve patient care (222). Integrating PROs within national clinical registries conveys additional benefits, enabling the evaluation of interventions at a national level from a patient-centred perspective, comparison of PROs within specific sub-groups of patients, and across national populations. These benefits have been observed through the NHS PROMs programme and data-linkage with the National Joint Registry in the UK (223-229).

There are several national colorectal cancer clinical registries (230), including NBOCA and the COloRECTal cancer data repository (CORECT-R) in the UK. NBOCA is a mandatory national audit of all patients diagnosed with colorectal cancer in England and Wales, it aims to assess quality of care and clinical outcomes (231). The introduction of NBOCA has had a number of benefits, from mapping variation in care delivery and outcomes at a regional level (232-234) and in relation to specific patient characteristics (235-239), through to documenting the impact of the COVID-19 pandemic on colorectal cancer care (231, 240-242). CORECT-R was created to facilitate access to curated

colorectal cancer linked datasets for researchers undertaking projects to improve outcomes in this disease setting (243), and includes access to PRO data from the Cancer Survivors in England 2013 PROMs survey (244, 245). CORECT-R has led to several research outputs with a particular focus on supporting earlier diagnosis (246-248) and tackling inequalities in treatment and outcomes (249-254). Data from the 2013 PROMs survey has also previously been linked to NBOCA (255). In the context of cancer care, capturing PROs is particularly important given the potential impact of treatments such as surgery and oncological treatments on HrQoL, and is highly valued by patients (15). The inclusion of PROs within cancer registries enables evaluation of patient-centred outcome data on a large scale.

PRC and LRRC differ considerably both in their natural history and treatment. There were 7,486 new cases of PRC reported in England and Wales from April 2020 to March 2021, with an estimated incidence of 732,210 cases worldwide in 2020 (256). There are a range of curative treatment strategies for PRC, including oncological treatments such as radiotherapy with or without chemotherapy, and surgery, including both major resection and local excision. For patients undergoing major resection for PRC, complete circumferential resection margin rates are reported to be greater than 90% (231, 257-262), with 5-year survival rates of over 70% following surgical resection (263-265). Conversely, LRRC occurs in less than 10% of cases following PRC resection (2-6) and curative treatment approaches in this setting are largely limited to radical surgical resection. R0 resection rates in LRRC are reported at 60.1 – 82.6% at highly specialist centres (50, 51, 54, 165), with this subgroup of patients achieving 5-year survival rates of 43-63% (50-54). The PelvEx collaborative data from 27 international centres reports a R0 resection rate of 55.4% with associated 5-year survival rates of 28.2% (35).

The clinical differences between PRC and LRRC are evident, and both are known to have a significant impact on HrQoL (97, 103, 104, 266-270), however the differences in the degree of impact on HrQoL are less clearly documented. Current evidence suggests that patients with LRRC have been reported to experience a further depreciation in their HrQoL when compared to patients with PRC (176), particularly during the initial months following surgery (173). This is unsurprising given that treatment, particularly curative surgical resection, is generally more complex due to its re-operative and radical nature, with high levels of post-operative morbidity (25, 65-68). Registries including HrQoL data offer an efficient means to assess potential differences in both clinical outcomes and PROs between these patient groups at a population-level. One of the key difficulties in comparing PROs is the availability of data collected using the same measures and the utilisation of measures which have been validated for use in specific contexts. The EORTC QLQ-C30 and EORTC QLQ-CR29 modules and FACT-C measure, are some of the most commonly used PROMs in LRRC, as described in chapter 2 of this thesis. This is primarily due to the lack of validated disease-specific measures for LRRC (157). The availability of PRO data, utilising measures which can be directly compared between these patient groups, could offer clinically valuable insights. There have been no recent studies comparing patients with PRC and LRRC in the UK. Additionally, the CORECT-R PROMs data has not been used to compare outcomes between these two groups of patients. Chapter 4 of this thesis describes the psychometric analysis of the LRRC-QoL in a combined cohort of patients from the UK and Australia. In order to analyse the convergent validity of the LRRC-QoL, data was collected utilising the FACT-C (108). This aim of this study was to assess cross-sectional differences in HrQoL in patients with PRC and LRRC; utilising the FACT-C to quantify HrQoL differences in these two patient groups in the context of a UK registry-based study utilising data from CORECT-R and the LRRC-QoL development and validation study.

3.1.1 Objectives

To compare scores for the FACT-C Colorectal Cancer Subscale between patients with primary and LRRC.

3.2 Methods

A propensity score matched cohort analysis was undertaken utilising cross-linked data from CORECT-R and the LRRC-QoL datasets, to compare cross-sectional HrQoL outcomes in patients with PRC and LRRC.

3.2.1 Data Extraction

3.2.1.1 LRRC-QoL Dataset

The data regarding patients with LRRC was collected as part of a study validating the LRRC-QoL in a combined UK and Australian cohort (108). This study includes only the UK patients from this cohort as the CORECT-R database only includes patients from the UK. The LRRC-QoL study was approved by the Yorkshire and the Humber Research Ethics Committee (REC) (reference: 12/YH/0518). Participants were recruited between January 2015 and September 2016 from three centres in the UK. The eligibility criteria for inclusion in the LRRC-QoL study were age ≥ 18 years, with an existing resectable LRRC either currently receiving neoadjuvant treatment or having undergone surgical treatment or non-surgical palliative treatment within the last two years, in addition to being able provide written, informed consent. Patients who had declined treatment or who were considered too frail to pursue surgical and/or oncological treatment were excluded.

The dataset includes 80 patients, for which the following data fields were extracted:

- Gender,
- Age,
- Ethnicity,
- Demographic details: marital status, education, employment,
- Details regarding PRC: date of surgery, operation, neoadjuvant treatment, TNM staging, margin status, adjuvant treatment,
- Interval between primary and recurrence,
- Details regarding LRRC: mode of detection, pattern of disease, presence of metastases, treatment intent, oncological treatments, date of surgery, operation, margin status, current disease status,
- Itemised FACT-C responses.

3.2.1.2 The CORECT-R Dataset

The CORECT-R research database was approved by the South West - Central Bristol REC (reference: 18/SW/0134). The CORECT-R database includes data collected during the Cancer Survivors in England 2013 PROMs survey, including self-reported clinical and demographic characteristics (244). Previous data-linkage enabled extraction specifically of patients with a history of PRC, however further clinical data-linkage has not been undertaken. The eligibility criteria for inclusion in this survey were patients age > 16 having survived 12 to 36 months after a diagnosis of colorectal cancer in 2010 or 2011 and treated in the National Health Service (NHS). The survey was administered by NHS England.

The following variables were extracted from the CORECT-R database including only patients who had undergone surgical resection for PRC:

- Sex,
- Age,
- Employment status,
- Length of time since completion of initial treatment for colorectal cancer,
- Response to treatment (in remission, recurrence, etc),
- Type of treatment (surgery, radiotherapy, chemotherapy),
- Site of neoplasm,
- Stoma presence at time of completion of questionnaire,
- Patient reported outcomes – itemised FACT-C Colorectal Cancer Subscale scores.

3.2.2 Outcome Assessment

The primary outcome was the FACT-C Colorectal Cancer Subscale (CCS). The FACT-C is a disease-specific PROM measuring QoL in patients with primary colorectal cancer, demonstrating robust psychometric properties (201). The FACT-C CCS is a scale within the FACT-C which consists of 7 heterogenous items measuring cancer-specific concerns unique to colorectal cancer patients, including swelling or stomach cramps, weight loss, control over bowels, the ability to digest food, diarrhoea, appetite, and body image (201). This measure was chosen for comparison as it was utilised in both the LRRC-QoL study and the Cancer Survivors in England 2013 PROMs survey and is disease-specific for patients with colorectal cancer. The full FACT-C measure was not included in the Cancer Survivors in England 2013 PROMs survey and therefore this data was not available for comparison. Scoring was undertaken as per the FACT-C guidelines, scores range from 0-28, with a higher score indicating lower symptom burden and better HrQoL (271).

3.2.3 Statistical Analysis

Propensity score matching was undertaken using nearest neighbour replacement to match a cohort of patients with PRC to the cohort of 80 LRRC patients in a 1:1 ratio, this ratio was selected due to its low risk of bias (272). Two covariates were used for propensity matching: age and sex, these covariates were chosen to ensure similar demographic groups of patients for comparison. Most of the clinical data extracted from CORECT-R regarding the 2013 PROMs survey was self-reported, for this reason, it was not possible to match clinical data categories as they were reported differently in each group. Other demographic characteristics were also recorded in different categories which prevented further matching. A descriptive analysis of all clinical and demographic data was reported for both groups. Data completeness for the FACT-C CCS data was assessed and missing data were handled with half-mean imputation (273, 274).

The scores for the FACT-C CCS were compared between patients with PRC and LRRC using independent t-tests, with p values <0.05 considered statistically significant; higher FACT-C scores denote better QoL. Cohen effect sizes were calculated to allow for comparison of the magnitude of differences in scores, effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large (275). Minimal clinically important differences (MCID) have been reported for the FACT-C CCS as 2-3 points (276) and were used to inform interpretation of the results from a clinical perspective.

3.2.4 Patient and Public Involvement

Patient and public involvement (PPI) work was undertaken during the development of this study, a PPI focus group meeting was held in May 2022 with two patients with a

history of LRRC (further information regarding the formation of the PPI group is included in chapter 10). The study proposal was discussed with the group, they were generally supportive of the aims of the study, however, felt it was important that the focus of the project centred on how this information could be used to drive improvements in patient care in the future. The PPI group also reviewed a proposed lay summary for the study (see Appendix 2), they found it easy to understand and did not find any of the words or phrases to be too medical or unintelligible, they felt that it provided a good and accessible explanation of the project.

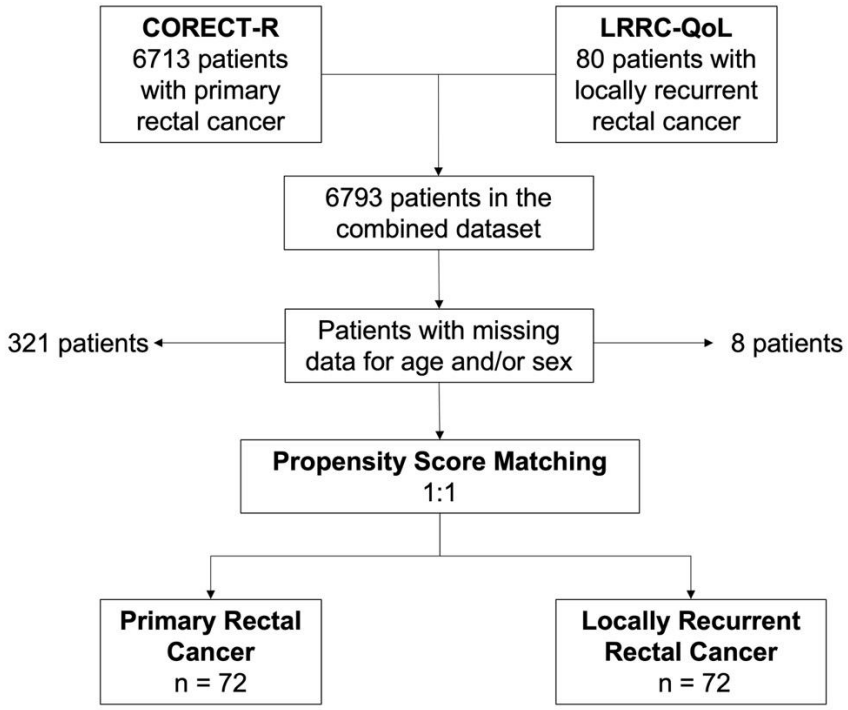
The study results were presented to the CORECT-R Patient-Public Group in October 2022, the group were supportive of the project and felt the findings would be useful for patients with LRRC. They felt this information would be particularly useful at the time of their diagnosis as they felt communication between clinicians and patients was particularly important at this timepoint and that reference to QoL outcomes would be helpful to inform this discussion. They felt that the lack of comparison of general QoL outcomes such as daily activities and ability to exercise, was a limitation of the study. They also suggested that questionnaires such as the FACT-C would be very useful as a prompt or guide in general practitioner (GP) or clinic appointments to guide discussions between clinicians and patients.

3.3 Results

A total of 6713 patients who had undergone surgical resection for PRC were identified from the CORECT-R database and were matched in a 1:1 ratio to the 80 patients in the

LRRC-QoL dataset, resulting in 72 patients in each group (see Figure 3.1). Eight patients in the LRRC group had missing age data and could not be matched.

Figure 3.1: Summary of propensity score matching



3.3.1 Clinical and Demographic Characteristics

Table 3.1 details the clinical and demographic characteristics for matched cohorts, there were 54 (75.0%) male patients with a median age of 65.3 years in both cohorts following matching. Most patients with PRC reported having completed treatment between 1 and 5 years ago at the time of participation (n=56, 77.78%). The UK patients with LRRC had all been diagnosed between 3 to 24 months of participating. The majority of patients (>90%) included in both cohorts were of white ethnicity (data not shown due to small numbers). Participants were most commonly retired, (n=41 (56.9%) in PRC and n=42 (58.3%) in LRRC). Most of the patients with PRC had undergone surgery, (n=68, 94.4%), with the majority of these receiving neoadjuvant or adjuvant treatments (n=53, 77.9%).

Thirty-four (47.2%) patients with LRRC had undergone surgery. At the time of participation, 62.5% (n=45) of patients with PRC reported having a stoma, compared with 44.4% (n=32) of the patients with LRRC, data regarding type of stoma (ileostomy vs colostomy, temporary vs permanent) were not collected. In terms of disease status at the time of participation, the majority of patients with PRC reported that their disease had responded fully to treatment (n=54, 75.0%), whereas 29.2% (n=21) of patients with LRRC were disease free at the time of participation.

Table 3.1: Clinical and demographic characteristics

	Primary Rectal Cancer (%)	**Locally Recurrent Rectal Cancer (%)**
Gender	**(Self-reported)** Male 54 (75.0) Female 18 (25.0)	**(Self-reported)** Male 54 (75.0) Female 18 (25.0)
Mean Age (SD)	65.26 (9.26)	65.26 (9.26)
Employment status	**(Self-reported)** Full time or part time employment 16 (22.2) Unemployed – seeking work 0 (0.0) Unemployed – unable to work 6 (8.3) Retired 41 (56.9) Other 5 (6.9) Unknown 4 (5.6)	**(Self-reported)** Full time or part time employment 5 (6.9) Unemployed 1 (1.4) Sick Leave 8 (11.1) Retired 42 (58.3) Self-employed 12 (16.7) Unknown 4 (5.6)
Length of time since completion of initial treatment for primary colorectal cancer	**(Self-reported)** Less than 12 months 15 (20.8) More than 12 months 57 (79.2)	**N/A**
Treatment for PRC	**(Self-reported)** Surgery only 15 (20.8) Radiotherapy only 1 (1.4) Surgery and radiotherapy 11	**(Clinician-reported)** Surgery only 14 (19.4) Radiotherapy only 0 (0.0) Surgery and radiotherapy 0 (0.0)

	(15.3) Surgery and chemotherapy 12 (16.7) Surgery, radiotherapy, and chemotherapy 30 (41.7) Radiotherapy and chemotherapy 3 (4.2)	Surgery and chemotherapy 15 (20.8) Surgery, radiotherapy, and chemotherapy 2 (2.8) Radiotherapy and chemotherapy 0 (0.0) Surgery and chemoradiotherapy 9 (12.5) Surgery, chemoradiotherapy, and chemotherapy 13 (18.1) Unknown 19 (26.4)
Presence of a stoma	**(Self-reported)** Soma present 45 (62.5) Stoma reversed 20 (27.8) No stoma 4 (5.6) Unknown 3 (4.2)	**(Self-reported)** Stoma present 32 (44.4) No stoma 40 (55.6)
Mode of detection of LRRC	**N/A**	**(Clinician-reported)** Surveillance 42 (58.3) Symptomatic 12 (16.7) Unknown 18 (25.0)
Pattern of LRRC	**N/A**	**(Clinician-reported)** Anterior 5 (6.9) Central 21 (29.2) Lateral 17 (23.6) Posterior 11 (15.3) Unknown 18 (25.0)
Presence of metastases in LRRC	**N/A**	**(Clinician-reported)** Yes 10 (13.9) No 44 (61.1) Unknown 18 (25.0)
Treatment intent for LRRC	**N/A**	**(Clinician-reported)** Curative 34 (47.2) Palliative 20 (27.8) Unknown 18 (25.0)
Margin status following surgery for LRRC (n=34)	**N/A**	**(Clinician-reported)** R0 21 (61.7) R1 11 (32.4) Unknown 2 (5.9)

Disease status at time of participation	**(Self-reported)** Responded fully 54 (75.0) Cancer treated but still present or has come back 7 (9.7) Not certain what is happening 9 (12.5) Unknown 2 (2.8)	**(Clinician-reported)** Disease free 21 (29.2) Distant disease recurrence 3 (4.2) Local disease recurrence 10 (13.9) Unknown 38 (53.8)

3.3.2 Data Completeness

Table 3.2 demonstrates the data completeness for the items within the FACT-C Colorectal Cancer Subscale for the propensity-matched cohorts each containing 72 patients, missing data for the other items were handled with half-mean imputation.

3.3.3 FACT-C Colorectal Cancer Subscale

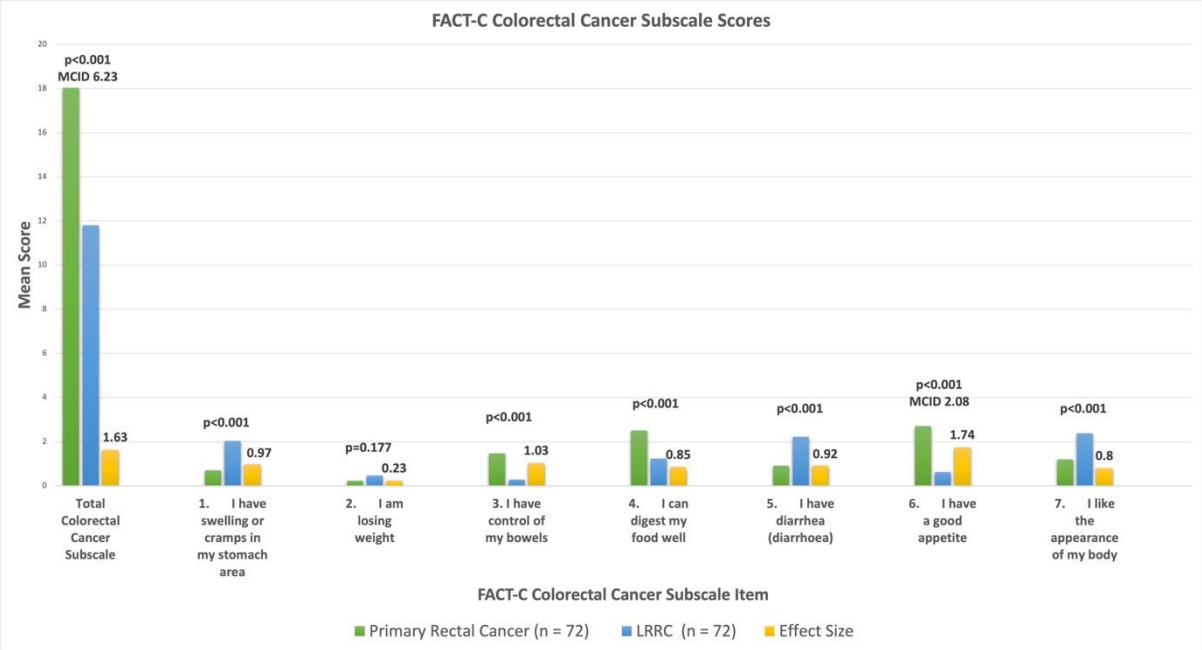
The mean scores for the overall FACT-C CCS and its constituent items can be found in Table 3.2 and Figure 3.2. Overall, the FACT-C CCS scores were significantly higher, denoting better QoL, in patients with PRC when compared with LRRC, from both a statistical ($p<0.001$, ES 1.63) and clinically meaningful standpoint with an MCID of 6.23. At an item level, patients with LRRC reported statistically significant worse levels of swelling or cramps in the stomach area (item 1, $p<0.001$, ES 0.97), worse ability to digest their food well (item 4, $p<0.001$, ES 0.85), and poor control over their bowels ($p<0.001$, ES 1.03), though not clinically significant. Patients with LRRC reported experiencing more diarrhoea (item 5, $p<0.001$, ES 0.92) and worse appetite from a both a statistical and clinical standpoint with a MCID of 2.08 points (item 6, $p<0.001$, ES 1.74). There were no significant differences in weight loss from a statistical or clinically meaningful perspective (item 2, $p=0.177$, ES 0.23). Finally, patients with LRRC reported statistically

significant greater satisfaction with the appearance of their body (item 7, $p<0.001$, ES 0.80).

Table 3.2: Data completeness and comparison of FACT-C CCS in the propensity-matched cohorts

Scale/ Item	**Primary Rectal Cancer**				**Locally Recurrent Rectal Cancer**				**p Value**	**Effect Size**	**MCID (2-3)**
	N	**Missing (%)**	**Mean**	**SD**	**N**	**Missing (%)**	**Mean**	**SD**			
Total Colorectal Cancer Subscale	72	16 **(22.2)**	18.03	4.77	72	3 **(4.2)**	11.80	2.55	**<0.001**	**1.63**	**YES (6.23)**
1. I have swelling or cramps in my stomach area	72	2 **(2.8)**	0.70	1.05	72	0 **(0.0)**	2.03	1.61	**<0.001**	**0.97**	NO (1.33)
2. I am losing weight	72	4 **(5.6)**	0.23	0.56	72	0 **(0.0)**	0.46	1.32	0.177	0.23	NO (0.23)
3. I have control of my bowels	72	11 **(15.3)**	1.47	1.49	72	0 **(0.0)**	0.28	0.65	**<0.001**	**1.03**	NO (1.19)
4. I can digest my food well	72	2 **(2.8)**	2.51	1.53	72	1 **(1.4)**	1.23	1.48	**<0.001**	**0.85**	NO (1.28)
5. I have diarrhea (diarrhoea)	72	3 **(4.2)**	0.91	1.22	72	0 **(0.0)**	2.22	1.60	**<0.001**	**0.92**	NO (1.31)
6. I have a good appetite	72	1 **(1.4)**	2.70	1.36	72	2 **(2.8)**	0.62	0.99	**<0.001**	**1.74**	**YES (2.08)**
7. I like the appearance of my body	72	2 **(2.8)**	1.19	1.20	72	0 **(0.0)**	2.38	1.60	**<0.001**	**0.80**	NO (1.19)

Figure 3.2: FACT-C CCS scores



In relation to the scores for the overall FACT-C CCS, items 3, 4, 6, and 7, a higher raw score indicates better HrQoL. In terms of items 1, 2, and 5, a higher raw score indicates worse HrQoL.

3.4 Discussion

The results of this study demonstrate that patients with LRRC reported significantly worse overall scores in the FACT-C CCS from both a statistical and clinical standpoint, denoting worse colorectal-cancer specific QoL when compared to patients with PRC in the context of a UK registry-based study. The responses to the individual items in the CCS also indicate that patients with LRRC experience worse abdominal swelling or cramps, worse digestion and appetite, and higher levels of diarrhoea. Conversely, patients with LRRC reported greater satisfaction with their appearance. The study demonstrates the ability to utilise existing clinical data from registries to demonstrate HrQoL differences between patients with PRC and LRRC.

This study highlights several benefits to accessing national PROMs survey data via CORECT-R. The ability to access this data for research purposes offers an efficient means to further interrogate the impact of colorectal cancer on HrQoL. It also facilitates comparison with other subgroups of patients, as reported in this study, through combining with LRRC-QoL study data. One of the key limitations of the CORECT-R dataset is the paucity of clinical data contained in the PROMs survey data. This limits the ability to examine these HrQoL outcomes in relation to clinical characteristics and outcomes. There are several challenges related to data-linkage across registries, including regulatory requirements, data protection and privacy preservation, and methodological challenges related to linkage, such as the availability of a common identifier across different datasets (222, 277). The availability of detailed outcome data is another challenge; cancer progression/recurrence, including LRRC, is not currently routinely captured in UK registries. However, this is changing with an increasing focus on this group of patients in NBOCA, with pelvic exenteration surgery being reported from 2019 for patients with locally advanced PRC, alongside the inclusion of advanced and recurrent disease management within the annual organisational survey (278). Ultimately, prospective HrQoL outcome reporting in patients with PRC, including those who go on to develop LRRC, would offer much greater insight into the impact of these conditions. Integrating prospective PRO data collection within existing colorectal cancer registries such as NBOCA or CORECT-R would further enhance their utility, particularly in facilitating research regarding HrQoL. However, the realities of collecting data in this way and maintaining high response rates present many challenges and are unlikely to be feasible until routine PRO data collection is mandated and fully integrated into existing clinical care pathways (223, 279).

From a clinical standpoint, the findings of this study confirm those of previous studies in the context of a UK cohort, demonstrating reduced HrQoL in patients with LRRC compared with PRC. In relation to outcome measures, FACT-C is commonly used to report HrQoL in both PRC and LRRC. FACT-C has not been validated for use specifically in patients with LRRC, though does contain a proportion of the HrQoL issues that have been identified as relevant to this patient group (157). The ability of FACT-C CCS to discriminate between these two groups of patients also suggests that it is sufficiently sensitive to detect a higher burden of symptoms in patients with LRRC. FACT-C CCS relates predominately to gastrointestinal symptoms, including abdominal swelling or cramps, control over the bowels, digestion, appetite, and diarrhoea. The results suggest that patients with LRRC can anticipate a greater frequency of gastrointestinal symptoms when compared with experiences during and after treatment for PRC. Radical surgery in the form of pelvic exenteration for patients with pelvic malignancy, including rectal and gynaecological malignancy, has been shown to lead to an initial deterioration in gastrointestinal symptoms, as measured by the EORTC QLQ-C30 and FACT-C, followed by improvement and return to baseline by 6-24 months (99). The majority of patients with LRRC recruited to the study were either receiving treatment or had recently undergone surgery, which is reflected in their worse CCS scores. Curative treatment strategies for LRRC are predominately surgical, frequently extensive and by their nature re-operative; often involving further resection of the gastrointestinal tract in addition to resection of the pelvic disease. The longer-term impact demonstrated here in patients with LRRC may be a result of chronic gastrointestinal dysfunction following these procedures. Other treatments for LRRC, such as radiotherapy and chemotherapy can also cause significant short-term gastrointestinal symptoms and longer term issues such as radiation enteritis which can have a significant impact on function (280).

This study has several strengths, including the use of national-level data and propensity score matching to control for potential confounding. The utilisation of MCIDs offers a clinical interpretation of the study results in addition to a traditional statistical approach and is likely to be more meaningful to patients. The cross-sectional nature of this study means it is impossible to offer direct comparison at specific time points, however, it gives a snapshot comparison of QoL outcomes, indicating that patients with LRRC experience a greater degree of colorectal-cancer specific symptoms. There are some limitations to this study, including the high rates of missing data and reduced availability of clinical data in patients with PRC due to it not being fully cross-linked within the CORECT-R dataset, as described. This also affected capacity to propensity score match for additional characteristics. Utilising the full FACT-C measure would have offered a better measure of overall QoL, however this was not possible as it was not included in full in the Cancer Survivors in England 2013 PROMs survey (244). The study compares data collected in 2013 from cancer survivors with PRC to data collected in 2015-2016 from UK patients with LRRC a median of 14 months following their diagnosis. The different timing of recruitment in relation to treatment phase may be a factor in the worse outcomes observed in the LRRC cohort. However, in relation to the timeframe of the two studies, treatment approaches for both PRC and LRRC in the UK did not change significantly between 2013 and 2016.

The findings of this study confirm that UK patients with LRRC also experience reduced HrQoL when compared with patients with PRC. This is a significant addition to the current literature as outcomes reported from individual countries may not be internationally generalisable, given the geographical variation in treatment pathways and guidelines, and associated variation in outcomes reported across high-income countries for patients with rectal cancer (281). Though the FACT-C has not been validated for use

in patients with LRRC (157), this study demonstrates its ability to quantify clinically meaningful differences in HrQoL in patients with PRC and LRRC. Existing evidence reporting HrQoL in LRRC utilising FACT-C should therefore not be disregarded, given this measure is able to elucidate colorectal specific HrQoL differences in LRRC. However, there is evidently an ongoing need for a disease-specific measure to comprehensively assess the HrQoL issues relevant to patients with LRRC. This study also highlights the benefits and areas for future work in the inclusion of PROMs data within national colorectal cancer clinical registries. These registries represent an important area of work within this field and will hopefully facilitate both clinical and PRO research in patients with advanced and recurrent colorectal cancer in the future.

3.5 Conclusion

This study establishes the ability to efficiently compare PROs in patients with PRC and LRRC through linking data available via registries to existing clinical data. The results build on existing evidence regarding HrQoL differences between these patient groups; as patients with LRRC reported significantly lower overall scores in the FACT-C CCS from both a statistical and clinical perspective, indicating they experience worse overall colorectal-cancer specific issues when compared with patients with PRC. The following chapters of this thesis aim to build upon this evidence, focusing on contributing to the evidence base regarding QoL and survivorship data in patients with LRRC.

Chapter 4 Psychometric Analysis of the LRRC-QoL in a UK and Australian Cohort

4.1 Introduction

Testing the psychometric properties of a PROM is an essential step in its development to ensure the creation of a credible and valid measure of the intended construct of interest. During the development of the LRRC-QoL, a cross-sectional cohort study was undertaken in the UK and Australia to evaluate the psychometric properties of the LRRC-QoL (108). A psychometric analysis of the questionnaire was undertaken in a cohort of 80 patients recruited from the UK (108), the Australian results were not included in this analysis due to ongoing recruitment.

Recruitment in Australia completed in September 2019 and the psychometric analysis described in this chapter is a result of combining the Australian cohort with the previously analysed UK data to report the definitive psychometric analysis of the LRRC-QoL questionnaire. The hypothesised scales for the LRRC-QoL described in this analysis represent the original hypothesised scales prior to the analysis undertaken in the UK cohort (108). The analysis described in this chapter represents the first step in validating the LRRC-QoL questionnaire; enabling the LRRC-QoL to be used in clinical settings to monitor HrQoL over the course of treatment for LRRC and in academic settings to report HrQoL outcomes in clinical trials for LRRC in both the UK and Australia.

4.2 Methods

Recruitment to the study was undertaken by Harji et al. and is described in greater detail elsewhere (108). Patients were recruited from 5 UK and 2 Australian sites. Patients with a diagnosis of LRRC were invited to participate in a cross-sectional observational study during which a self-complete questionnaire pack was sent to all eligible patients, this contained the LRRC-QoL tool in addition to other quality of life measures; the EORTC QLQ-CR29 and FACT-C to complete and return. All participants were then invited to complete the same questionnaires again 10-14 days later for the test-retest test. Data were also collected for socio-demographic and clinical details.

4.2.1 Data Analysis

All data were analysed using SPSS Statistics for Mac, version 26 (IBM Corp., Armonk, N.Y., USA). Descriptive analysis was undertaken for the demographic and clinical data. A psychometric analysis of the LRRC-QoL was undertaken in accordance with the methods described by Harji (108) and is summarised in Table 4.1. Clinical characteristics were compared between participants recruited from the UK and Australia using the chi squared test.

Table 4.1: Data analysis plan

	4.2.1.1 Definitions	**4.2.1.2 Methods**
4.2.1.3 Data Completeness	**4.2.1.4 Acceptable levels of data:** • <10% missing data at an item level • <50% missing data for total computable scale scores	**4.2.1.5 Half-mean Imputation** Missing data were handled using half-mean imputation (273, 274), provided the criteria for acceptable levels of missing data were met.

<table>
<tr><td></td><td colspan="2"><80% for single scores to limit potential for floor/ceiling effects</td></tr>
<tr><td rowspan="6">4.2.1.6 Scale Structure</td><td colspan="2">4.2.1.7 MULTI-TRAIT ANALYSIS
The unidimensionality of the items within the proposed scales and the proposed scale structure of the LRRC-QoL were assessed using multi-trait analysis.</td></tr>
<tr><td>4.2.1.8 Item Internal Consistency
Item internal consistency assesses the extent to which items within a scale are related to each other and to the construct being measured.</td><td>4.2.1.9 Item Intercorrelation
The statistical correlation between items within a scale, it should be between 0.3-0.7 to demonstrate item internal consistency.

4.2.1.10 Item-to-scale correlation
The statistical correlation between one item and the sum of the other items within the scale. Values should be of a similar magnitude with a recommended value of 0.3.</td></tr>
<tr><td>4.2.1.11 Item Discriminant Validity
Item discriminant validity assesses whether items within a scale correlate more highly with their own hypothesised scale than with another scale measuring a different concept.</td><td>Two standard errors were used to define the amount by which this would be a significant degree of correlation.</td></tr>
<tr><td colspan="2">4.2.1.12 EXPLORATORY FACTOR ANALYSIS
Exploratory factor analysis (EFA) was used to test scale stability and to identify clusters of items measuring similar concepts.</td></tr>
<tr><td>Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy and Bartlett’s Test of Sphericity were used to establish whether the data was suitable for EFA.</td><td>4.2.1.13 KMO Measure of Sampling Adequacy
KMO statistic varies between 0 and 1, a value close to 1 indicates that patterns of correlations are compact [4]. A value ≥0.5 is considered suitable for factor analysis.

4.2.1.14 Bartlett’s Test
Bartlett’s test examines whether a correlation matrix is different from an identity matrix, meaning it is significant when the correlations between variables are significantly different from zero [4].</td></tr>
</table>

4.2.1.15 Reliability	Reliability is the extent to which scores in an instrument reflect the 'true' score on the construct of interest [4]. Reliability is measured by the internal consistency of a scale and reproducibility of the questionnaire using the test-retest measure.	**4.2.1.16 Internal Consistency** Internal consistency was measured using Cronbach's Alpha, it is considered good when Cronbach's Alpha is >0.7. **4.2.1.17 Test-Retest Measure** Test-retest measures the stability of a PROM over a period where there is no clinical change. Intraclass Correlation (ICC) was used to assess this, an ICC score of ≥0.7 is recommended.
4.2.1.18 Validity	**4.2.1.19 Construct Validity** The extent to which an instrument measures the construct it intended to.	Assessed through multi-trait analysis.
	4.2.1.20 Convergent Validity A measure of the correlation between tools measuring the same constructs.	Hypotheses were made in relation to the convergent validity of the LRRC-QoL with the EORTC CR29 and FACT-C. These hypotheses were assessed using Pearson's Product Moment Correlation. Pearson's values of greater than 0.45 are considered highly correlated.
	4.2.1.21 Known Groups Comparison Establishing whether the LRRC-QoL can identify differences based on clinical characteristics.	The independent t-test was used to compare mean scores between 2 groups and ANOVA was used to compare mean scores in groups >2.

4.3 Results

Patient demographics and clinical characteristics can be found in Table 4.2. One hundred and seventeen patients were recruited to the study, 80 from the UK and 37 from Australia. There were 84 male patients (71.8%) and median age was 66 (IQR 11.75). Median interval between PRC and recurrence was 2 years (IQR 3.0). Seventy-four (63.2%) patients were treated with curative intent and 21 (17.9%) were treated with palliative

intent, with missing data for 22 (18.8%) patients. Palliative intent was defined as non-surgical management (108).

Comparing clinical characteristics between patients recruited from the UK and Australia showed a significant difference in several categories. Patients recruited from Australia were more likely to present with LRRC symptomatically (40% vs. 15%, p=0.009). All patients recruited from Australia were treated with curative intent (100% vs. 46.3%, p<0.0001). There was a significant difference in disease status at the time of recruitment to the study, with a higher proportion of Australian patients being disease free (56.8% vs. 27.5%, p=0.013).

Table 4.2: Patient demographics

Variable	**Responders (n=117) (%)**	**UK cohort (n=80) (%)**	**Australian cohort (n=37) (%)**	**Significance**
Gender				
Male	84 (71.8)	60 (75)	24 (64.9)	0.257
Female	33 (28.2)	20 (25)	13 (35.1)	
Median Age (IQR)	66.0 (11.75)	66.0 (10.75)	66.5 (15.75)	0.338
Ethnicity				
White	69 (59)	69 (86.3)	0 (0.0)	N/A
Black	5 (4.3)	5 (6.3)	0 (0.0)	
Asian	1 (0.9)	1 (1.3)	0 (0.0)	
Unknown	42 (35.9)	5 (6.3)	37 (100.0)	
Marital status				
Married	90 (76.9)	62 (77.5)	28 (75.7)	0.119
Living Common Law	5 (4.3)	5 (6.3)	0 (0.0)	
Widowed	3 (2.6)	3 (3.8)	0 (0.0)	
Separated	2 (1.7)	2 (2.5)	0 (0.0)	
Divorced	4 (3.4)	1 (1.3)	3 (8.1)	
Single	3 (2.6)	1 (1.3)	2 (5.4)	
Unknown	10 (8.5)	6 (7.5)	4 (10.8)	

Education status				
Secondary school	45 (38.5)	30 (37.5)	15 (40.5)	0.123
College	25 (21.4)	20 (25.0)	5 (13.5)	
University	27 (23.1)	20 (25.0)	7 (18.9)	
Other	9 (7.7)	3 (3.8)	6 (16.2)	
Unknown	11 (9.4)	7 (8.8)	4 (10.8)	
Employment status				
Self-employed	15 (12.8)	12 (15.0)	3 (8.1)	0.057
Home maker	1 (0.9)	0 (0.0)	1 (2.7)	
Full time employment	8 (6.8)	2 (2.5)	6 (16.2)	
Part time employment	6 (5.1)	3 (3.8)	3 (8.1)	
Unemployed	1 (0.9)	1 (1.3)	0 (0.0)	
Sick leave	10 (8.5)	9 (11.3)	1 (2.7)	
Retired	63 (53.8)	44 (55.0)	19 (51.4)	
Missing	13 (11.1)	9 (11.3)	4 (10.8)	
Interval between Primary and Recurrence (years)				
<1	9 (7.7)	5 (6.3)	4 (10.8)	0.549
1	19 (16.2)	14 (17.5)	5 (13.5)	
2	15 (12.8)	10 (12.5)	5 (13.5)	
3	9 (7.7)	6 (7.5)	3 (8.1)	
4	7 (6.0)	4 (5.0)	3 (8.1)	
5	8 (6.8)	4 (5.0)	4 (10.8)	
6	1 (0.9)	1 (1.3)	0 (0.0)	
7	1 (0.9)	1 (1.3)	0 (0.0)	
8	2 (1.7)	1 (1.3)	1 (2.7)	
20	1 (0.9)	0 (0.0)	1 (2.7)	
21	1 (0.9)	0 (0.0)	1 (2.7)	
Unknown	44 (37.6)	34 (42.5)	10 (27.0)	
Treatment for PRC				
Neoadjuvant treatment				
None	49 (41.9)	31 (38.8)	18 (48.6)	0.001
Short course radiotherapy	4 (3.4)	3 (3.8)	1 (2.7)	
Chemoradiation	32 (27.4)	22 (27.5)	10 (27.0)	
Chemotherapy	6 (5.1)	0 (0.0)	6 (16.2)	
Contact radiotherapy	1 (0.9)	1 (1.3)	0 (0.0)	
Unknown	25 (21.4)	23 (28.7)	2 (5.4)	

Operation for PRC				
Anterior resection	57 (48.7)	37 (46.3)	20 (54.1)	0.398
APER	15 (12.8)	9 (11.3)	6 (16.2)	
Composite abdominosacral	2 (1.7)	2 (2.5)	0 (0.0)	
Hartmann's	6 (5.1)	6 (7.5)	0 (0.0)	
Local excision	4 (3.4)	3 (3.8)	1 (2.7)	
Panproctocolectomy	1 (0.9)	0 (0.0)	1 (2.7)	
Pelvic exenteration	1 (0.9)	1 (1.3)	0 (0.0)	
Unknown	31 (26.5)	22 (27.5)	9 (24.3)	
TNM Staging PRC				
T1N0	4 (3.4)	4 (5.0)	0 (0.0)	
T2N0	8 (6.8)	8 (10.0)	0 (0.0)	
T2N1	4 (3.4)	2 (2.5)	2 (5.4)	
T3N0	15 (12.8)	13 (16.3)	2 (5.4)	
T3N1	22 (18.8)	16 (20.0)	6 (16.2)	
T3N2	6 (5.1)	3 (3.8)	3 (8.1)	
T4N0	9 (7.7)	5 (6.3)	4 (10.8)	
T4N1	7 (6.0)	6 (7.5)	1 (2.7)	
Unknown	42 (35.9)	23 (28.7)	19 (51.4)	
Margin status				
R0	65 (55.6)	50 (62.5)	15 (40.5)	0.002
R1	22 (18.8)	8 (10.0)	14 (37.8)	
Unknown	30 (25.6)	22 (27.5)	8 (21.6)	
Adjuvant treatment for PRC				
None	24 (20.5)	24 (30.0)	0 (0.0)	N/A
Chemoradiation	2 (1.7)	2 (2.5)	0 (0.0)	
Chemotherapy	31 (26.5)	31 (38.8)	0 (0.0)	
Unknown	60 (51.3)	23 (28.7)	37 (100.0)	
Locally Recurrent Rectal Cancer				
Mode of detection				
Symptomatic	27 (23.1)	12 (15.0)	15 (40.0)	0.009
Surveillance	60 (51.3)	46 (57.5)	14 (37.8)	
Unknown	30 (25.6)	22 (27.5)	8 (21.6)	
Pattern of LRRC				
Anterior	12 (10.3)	5 (6.3)	7 (18.9)	0.057
Central	25 (21.4)	22 (27.5)	3 (8.1)	

Lateral	27 (23.1)	19 (23.8)	8 (21.6)	
Posterior	20 (17.1)	12 (15.0)	8 (21.6)	
Unknown	33 (28.2)	22 (27.5)	11 (29.7)	
Presence of Metastatic disease				
Yes	12 (10.3)	11 (13.8)	1 (2.7)	0.179
No	71 (60.7)	46 (57.5)	25 (67.6)	
Unknown	34 (29.1)	23 (28.7)	11 (29.7)	
Treatment Intent				
Curative	74 (63.2)	37 (46.3)	37 (100.0)	0.000
Palliative	21 (17.9)	21 (26.3)	0 (0.0)	
Unknown	22 (18.8)	22 (27.5)	0 (0.0)	
Pre-operative Treatment				
None	9 (12.2)	9 (24.3)	0 (0.0)	N/A
Chemoradiation	19 (25.7)	19 (51.4)	0 (0.0)	
Chemotherapy	1 (1.4)	1 (2.7)	0 (0.0)	
Radiotherapy	2 (2.7)	2 (5.4)	0 (0.0)	
Unknown	43 (58.1)	6 (16.2)	37 (100.0)	
Palliative Treatment				
Chemoradiation	4 (19.0)	4 (19.0)	0 (0.0)	N/A
Chemotherapy	16 (76.2)	16 (76.2)	0 (0.0)	
Surgery	1 (4.8)	1 (4.8)	0 (0.0)	
Margin Status				
R0	44 (37.6)	21 (26.3)	23 (62.2)	0.001
R1	18 (15.4)	14 (17.5)	4 (10.8)	
R2	1 (0.9)	0 (0.0)	1 (2.7)	
Unknown	54 (46.2)	45 (56.3)	9 (24.3)	
Post-operative Treatment				
Chemotherapy	11 (9.4)	8 (10.0)	3 (8.1)	0.191
None	46 (39.3)	27 (33.8)	19 (51.4)	
Unknown	60 (51.3)	45 (56.3)	15 (40.5)	
Current Disease Status				
Disease free	43 (36.8)	22 (27.5)	21 (56.8)	0.013
Distant disease recurrence	4 (3.4)	3 (3.8)	1 (2.7)	
Local disease recurrence	13 (11.1)	12 (15.0)	1 (2.7)	
Unknown	57 (48.7)	43 (53.8)	14 (37.8)	

4.3.1 Data Completeness

Tables 4.3 and 4.4 portray descriptive statistics for the LRRC-QoL at an item and scalar level. Several items in the LRRC-QoL did not fulfil the criteria of <10% missing data. These included items 5 and 6, regarding vaginal bleeding or discharge, and vaginal irritation with missing data rates of 15.2%. Items in the sexual function scale also had higher rates of missing data from 21.4-32.5%. These questions are of a personal nature and as such, higher rates of missing data were anticipated. These items were not removed from the LRRC-QoL as it was felt that they reflect important quality of life issues which are known to exhibit higher rates of missing data. Item 32, regarding frequency of consultations also had a high rate of missing data at 24.8%, this item was therefore excluded from the analysis. All items demonstrated response rates of <80% for single scores demonstrating low potential for floor/ceiling effects. Data completeness of >50% was observed for total computable scale scores for all the scales.

Table 4.3: Item level descriptive analysis

Symptom Scale	**N**	**Missing (%)**	**Mean**	**SD**	**Response Value Frequency (%)**			
					1	**2**	**3**	**4**
1. Abdominal pain	117	6 (5.1)	1.50	0.74	56 (47.9)	48 (41)	5 (4.3)	2 (1.7)
2. Back pain	117	5 (4.3)	1.77	0.95	48 (41.0)	39 (33.3)	19 (16.2)	6 (5.1)
3. Perianal/buttock pain	117	5 (4.3)	1.80	0.98	45 (38.5)	44 (37.6)	14 (12.0)	9 (7.7)
4. Rectal bleeding or discharge	117	5 (4.3)	1.45	0.85	73 (62.4)	23 (19.7)	13 (11.1)	3 (2.6)
5. Vaginal bleeding or discharge	33	5 (15.2)	0.35	0.61	22 (66.7)	5 (15.2)	1 (3.0)	0 (0.0)
6. Vaginal irritation	33	5 (15.2)	0.32	0.60	22 (66.7)	5 (15.2)	1 (0.9)	0 (0.0)
7. Urinary irritation	117	11 (9.4)	1.26	0.77	74 (63.2)	24 (20.5)	6 (5.1)	2 (1.7)
8. Urinary incontinence	117	5 (4.3)	1.50	0.84	66 (56.4)	33 (28.2)	9 (7.7)	4 (3.4)

9. Lower limb weakness	117	6 (5.1)	1.71	0.96	50 (42.7)	40 (34.2)	14 (12.0)	7 (6.0)
10. Difficulty in walking	117	4 (3.4)	1.83	1.00	47 (40.2)	42 (35.9)	13 (11.1)	11 (9.4)
11. Lower limb numbness	117	5 (4.3)	1.88	1.04	44 (37.6)	40 (34.2)	16 (13.7)	12 (10.3)
12. Pain/discharge from wounds	117	5 (4.3)	1.28	0.68	84 (71.8)	18 (15.4)	10 (8.5)	0 (0.0)
14. Problems caring for urostomy	24	0 (0.0)	0.32	0.68	12 (50.0)	11 (45.8)	1 (4.2)	0 (0.0)
15. Embarrassment from urostomy`	24	0 (0.0)	0.33	0.73	12 (50.0)	9 (37.5)	3 (12.5)	0 (0.0)
16. Dependent on others for caring for urostomy	24	0 (0.0)	0.26	0.61	19 (79.2)	4 (16.7)	1 (4.2)	0 (0.0)
18. Embarrassment from stoma	64	0 (0.0)	0.93	1.06	33 (51.6)	22 (34.4)	5 (7.8)	4 (6.3)
19. Problems caring for stoma	64	1 (1.6)	0.75	0.86	46 (71.9)	11 (17.2)	5 (7.8)	1 (1.6)
Psychological Impact Scale								
20. Dependence	117	7 (6.0)	1.74	0.93	43 (36.8)	47 (40.2)	14 (12)	6 (5.1)
21. Attractiveness	117	7 (6.0)	1.82	1.05	46 (39.3)	34 (29.1)	21 (17.9)	9 (7.7)
Sexual Function Scale								
22. Pain	117	38 (32.5)	0.92	0.88	59 (50.4)	14 (12)	3 (2.6)	3 (2.6)
23. Interest	117	25 (21.4)	1.44	1.16	44 (37.6)	28 (23.9)	11 (9.4)	9 (7.7)
24. Erectile function	84	20 (23.8)	1.56	1.68	14 (16.7)	11 (13.1)	10 (11.9)	29 (34.5)
25. Ejaculatory dysfunction	84	25 (29.8)	1.42	1.68	16 (19.0)	6 (7.1)	10 (11.9)	27 (32.1)
Future Perspective Scale								
26. Results	117	9 (7.7)	2.05	0.99	19 (16.2)	54 (46.2)	27 (23.1)	8 (6.8)
27. Future treatments	117	8 (6.8)	2.13	1.05	20 (17.1)	51 (43.6)	25 (21.4)	13 (11.1)
28. Uncertainty	117	6 (5.1)	2.41	0.89	14 (12.0)	54 (46.2)	27 (23.1)	16 (13.7)
Healthcare Services and Delivery								

29. Information	117	11 (9.4)	2.85	1.24	3 (2.6)	24 (20.5)	34 (29.1)	45 (38.5)
30. Knowledge	117	10 (8.5)	3.16	1.20	3 (2.6)	7 (6.0)	35 (29.9)	62 (53.0)
31. Tests	117	10 (8.5)	2.95	1.33	11 (9.4)	13 (11.1)	24 (20.5)	59 (50.4)
32. Frequency of consultations	117	29 (24.8)	2.40	1.61	6 (5.1)	14 (12.0)	25 (21.4)	43 (36.8)

Table 4.4: Scalar level descriptive analysis

Scale	Total No of Items in Scale	Data Completeness (%)	Possible Score Range	Observed Score Range	Mean Score	SD
Symptoms	17	96.6	10-68*	12-34	20.11	5.65
Psychological	2	94.9	2-8	2-8	3.78	1.44
Sexual Function	4	76.1	2-16	2-15	6.59	3.54
Future Perspective	3	94.0	3-12	3-12	6.90	2.24
Healthcare Services	4	90.6	4-16	4-16	12.79	2.80

***the minimum score for the Symptoms scale is 10 given that it contains items which are specific to certain patient groups; items 5 and 6 for women, items 14-16 for patients with a urostomy and items 18 and 19 for patients with a stoma.**

4.3.2 Multi-trait Analysis of the Hypothesised LRRC-QoL Scales

The multi-trait/multi-item correlation matrix is detailed in Table 4.5 and the item summary statistics are detailed in Table 4.6.

Table 4.5: LRRC-QoL hypothesised scales multi-trait/multi-item correlation matrix

	Symptom Scale	Psychological Function	Sexual Function	Future Perspective	Healthcare Services
Symptom Scale					
1. Abdominal pain	0.463	0.312	-0.202	0.154	0.021

2. Back pain	0.555	0.303	-0.096	0.144	0.032
3. Perianal/buttock pain	0.589	0.335	0.059	0.122	-0.026
4. Rectal bleeding or discharge	0.213	0.170	0.023	-0.005	-0.143
5. Vaginal bleeding or discharge	0.268	0.064	-0.638	0.085	-0.019
6. Vaginal irritation	0.224	0.104	-0.640	0.105	-0.046
7. Urinary irritation	0.127	0.152	0.164	0.086	-0.124
8. Urinary incontinence	0.350	0.149	-0.148	0.097	-0.152
9. Lower limb weakness	0.549	0.205	-0.007	-0.009	-0.006
10. Difficulty in walking	0.680	0.295	0.105	0.062	-0.028
11. Lower limb numbness	0.500	0.102	0.065	-0.101	0.074
12. Pain/discharge from wounds	0.170	-0.029	0.124	-0.105	-0.223
14. Problems caring for urostomy	0.434	-0.006	-0.070	-0.116	0.108
15. Embarrassment from urostomy`	0.402	0.057	-0.066	-0.063	0.184
16. Dependent on others for caring for urostomy	0.445	-0.011	-0.041	-0.121	0.079
18. Embarrassment from stoma	0.429	0.214	0.006	0.144	0.175
19. Problems caring for stoma	0.498	-0.005	-0.011	0.025	0.126
Psychological Function					
20. Dependence	0.318	0.768	-0.062	0.372	0.011
21. Attractiveness	0.262	0.829	-0.004	0.410	0.035
Sexual Function					
22. Pain	-0.113	-0.040	0.368	0.035	0.042
23. Interest	-0.277	-0.137	0.661	-0.014	-0.053
24. Erectile function	-0.071	0.036	0.877	-0.031	0.121
25. Ejaculatory dysfunction	-0.047	-0.028	0.881	0.018	0.016
Future Perspective					

26. Results	0.057	0.364	-0.010	0.866	-0.110
27. Future treatments	0.002	0.426	-0.058	0.882	-0.026
28. Uncertainty	0.145	0.485	0.060	0.864	0.028
Healthcare Services and Delivery					
29. Information	0.057	0.086	0.023	0.019	0.878
30. Knowledge	-0.020	0.039	0.105	0.006	0.835
31. Tests	0.011	-0.036	0.023	-0.107	0.858

Blue shading indicates results for item-to-scale correlation for the scale of interest. Orange shading indicates values of >0.4 for item discriminant validity.

Table 4.6: Item summary statistics

Scale	No of Items	Mean Item Intercorrelation	Item Discriminant Validity (Range of Scores)	Item to Total Correlations
Symptoms	17	0.115	-0.640 – 0.335	0.010 – 0.572
Psychological Function	2	0.278	-0.062 – 0.410	0.278
Sexual Function Female	2	0.635	-0.260 – 0.358	0.635
Sexual Function Male	2	0.511	-0.278 – 0.200	0.511
Future Perspective	3	0.638	-0.113 – 0.485	0.685 - 0.719
Healthcare Services	3	0.606	-0.223 – 0.175	0.619 - 0.719

4.3.2.1 Symptom Scale

There are 17 items and two skip questions within the hypothesised LRRC-QoL Symptom scale with a possible score range of 10-68. The minimum score of 10 is due to several questions being specific to certain patient groups: items 5 and 6 for women, items 14-16 for patients with a urostomy and items 18-19 for patients with a stoma.

Overall, the hypothesised symptom scale did not perform well in multi-trait scaling analysis. Five of the 17 items within the scale failed to meet the criteria for item-to-total

correlation of >0.3 (see Table 4.5), meaning that these items did not contribute equally to the total computable score for symptom scale.

The item intercorrelation matrix for the hypothesised symptom scale is shown in Table 4.7. Several groups of items, particularly those measuring similar groups of symptoms were highly intercorrelated, these included items 1-3 which relate to pain, namely abdominal pain, lower back and/or pelvic pain and pain in the buttocks/anal area/rectum, with item intercorrelation scores of 0.397-0.484. Other items which showed high intercorrelation included items 5 and 6 regarding gynaecological symptoms, with an intercorrelation score of 0.899, items 9-11 regarding the lower limbs and mobility had item intercorrelation of 0.481-0.663. Items 14-16 related to urostomies had scores of 0.769-0.883 and items 18-19 regarding stomas had a score of 0.616. These high intercorrelation values intimate homogeneity between the items listed which would be expected for items measuring similar symptoms.

Despite these groups of items which correlate highly with one another, many other items within the scale had item intercorrelation values of <0.3, indicating that they do not measure similar constructs, as required for items within the same scale to show item internal consistency. Although the Symptoms scale failed to demonstrate good item internal consistency, it did demonstrate good item discriminant validity with all values measuring <0.4.

Table 4.7: Symptom scale item intercorrelation matrix

	LRRC 1	LRRC 2	LRRC 3	LRRC 4	LRRC 5	LRRC 6	LRRC 7	LRRC 8	LRRC 9	LRRC 10	LRRC 11	LRRC 12	LRRC 14	LRRC 15	LRRC 16	LRRC 18	LRRC 19
1. Abdominal pain	1	0.446	0.397	0.175	0.225	0.292	0.209	0.231	0.122	0.252	0.081	0.021	-0.045	-0.008	-0.073	0.062	0.001
2. Back pain	0.446	1	0.484	0.156	0.163	0.162	0.074	0.159	0.351	0.380	0.105	0.065	0.024	-0.001	0.093	0.033	0.109
3. Perianal / buttock pain	0.397	0.484	1	0.327	0.009	0.125	0.101	0.197	0.194	0.445	0.094	0.126	0.061	0.113	0.042	0.154	0.083
4. Rectal bleeding / discharge	0.175	0.156	0.327	1	-0.071	-0.034	0.077	0.235	-0.069	0.137	-0.117	0.064	-0.002	-0.003	-0.055	-0.172	-0.117
5. Vaginal bleeding or discharge	0.225	0.163	0.009	-0.071	1	0.899	-0.144	0.125	0.040	-0.008	0.040	-0.165	0.045	0.029	-0.048	0.111	0.039
6. Vaginal irritation	0.292	0.162	0.125	-0.034	0.899	1	-0.168	0.087	-0.046	-0.039	-0.005	-0.165	-0.063	-0.031	-0.096	0.056	0.006
7. Urinary irritation	0.209	0.074	0.101	0.077	-0.144	-0.168	1	0.454	0.079	0.157	-0.057	0.142	-0.196	-0.218	-0.184	-0.116	-0.230
8. Urinary incontinence	0.231	0.159	0.197	0.235	0.125	0.087	0.454	1	0.213	0.251	0.131	0.080	-0.186	-0.167	-0.192	-0.089	-0.049
9. Lower limb weakness	0.122	0.351	0.194	-0.069	0.040	-0.046	0.079	0.213	1	0.663	0.537	-0.051	0.109	0.024	0.167	0.013	0.174
10. Difficulty in walking	0.252	0.380	0.445	0.137	-0.008	-0.039	0.157	0.251	0.663	1	0.481	0.016	0.162	0.090	0.201	0.057	0.189
11. Lower limb numbness	0.081	0.105	0.094	-0.117	0.040	-0.005	-0.057	0.131	0.537	0.481	1	-0.009	0.081	0.051	0.118	0.229	0.329
12. Pain/ discharge from wounds	0.021	0.065	0.126	0.064	-0.165	-0.165	0.142	0.080	-0.051	0.016	-0.009	1	0.010	-0.061	0.080	-0.012	0.197

14. Problems caring for urostomy	-0.045	0.024	0.061	-0.002	0.045	-0.063	-0.196	-0.186	0.109	0.162	0.081	0.010	1	0.845	0.883	0.225	0.303
15. Embarrassment from urostomy	-0.008	-0.001	0.113	-0.003	0.029	-0.031	-0.218	-0.167	0.024	0.090	0.051	-0.061	0.845	1	0.769	0.334	0.217
16. Dependence on others for caring for urostomy	-0.073	0.093	0.042	-0.055	-0.048	-0.096	-0.184	-0.192	0.167	0.201	0.118	0.080	0.883	0.769	1	0.207	0.383
18. Embarrassment from stoma	0.062	0.033	0.154	-0.172	0.111	0.056	-0.116	-0.089	0.013	0.057	0.229	-0.012	0.225	0.334	0.207	1	0.616
19. Problems caring for stoma	0.001	0.109	0.083	-0.117	0.039	0.006	-0.230	-0.049	0.174	0.189	0.329	0.197	0.303	0.217	0.383	0.616	1

Blue shading indicates correlation of an item with itself. Green shading indicates a correlation value of >0.3.

4.3.2.2 Psychological Scale

The hypothesised LRRC-QoL psychological scale consisted of two items, demonstrating mean item intercorrelation of 0.278 (Table 4.8) and equal item-to-total correlation, meaning that overall, this scale showed reasonable item internal consistency. On assessing item discriminant validity, most values indicate a lower rate of correlation with the other scales. However, there was one correlation of 0.410 between item 21 denoting physical attraction and the Future Perspectives scale, indicating that there may be some overlap between the constructs being measured.

Table 4.8 : Psychological scale item intercorrelation matrix

	20. Dependence	21. Attractiveness
20. Dependence	1	0.278
21. Attractiveness	0.278	1

4.3.2.3 Sexual Function

There were four items within the hypothesised Sexual Function scale, with two of these items relating specifically to male patients (items 24 and 25) and the analysis was undertaken specific to patient gender.

Analysis of responses from female patients showed mean item intercorrelation of 0.635 (Table 4.9) and equal item-to-total correlation thus illustrating good item internal consistency of the scale. Analysis for correlation with the other scales was undertaken using scale sums for only female patients and demonstrated good item discriminant validity (Table 4.10).

Table 4.9: Female Sexual Function scale item intercorrelation matrix

	22. Pain during sexual intercourse – Female	23. Interest in sex – Female
22. Pain during sexual intercourse	1	0.635
23. Interest in sex	0.635	1

Table 4.10: Multi-trait/multi-item correlation matrix of hypothesised scales for female participants

	Symptom Scale Female	Psychological Function Female	Sexual Function Female	Future Perspective Female	Healthcare Services Female
22. Pain during sexual intercourse - Female	-0.115	-0.260	0.924	0.358	0.196
23. Interest in sex - Female	-0.057	-0.189	0.882	0.188	0.009

Blue shading indicates item-to-scale correlation values for the Female Sexual Function Scale.

Regarding male patients, the analysis was undertaken for items 24-25 within the Sexual Function scale, demonstrating mean item intercorrelation of 0.511 (Table 4.11) and equal item-to-total correlation, indicating good item internal consistency. There was good item discriminant validity on comparing correlation between sum scale scores for male patients (Table 4.12).

Table 4.11: Male Sexual Function scale item intercorrelation matrix

	24. Erectile function	25. Ejaculatory function
24. Erectile function	1	0.511
25. Ejaculatory function	0.511	1

Table 4.12: Multi-trait/multi-item correlation matrix of hypothesised scales for male participants

	Symptom Scale Male	Psychological Function Male	Sexual Function Male	Future Perspective Male	Healthcare Services Male
24. Erectile function	0.138	0.200	0.747	0.070	0.174
25. Ejaculatory function	0.162	0.069	0.768	0.146	0.035

4.3.2.4 Future Perspective

The hypothesised Future Perspectives scale consisted of three items. On multi-trait analysis, the scale showed excellent item internal consistency with mean item intercorrelation of 0.638 (Table 4.13) and equal item-to-total correlation. However, on assessing item discriminant validity, the scale exhibited correlation scores of >0.4 with items 27 regarding future treatments and item 28 regarding uncertainty in the Psychological Function scale (Table 4.5).

Table 4.13: Future Perspective scale item intercorrelation matrix

	26. Results	27. Future treatments	28. Uncertainty
26. Results	1	0.666	0.620
27. Future treatments	0.666	1	0.630
28. Uncertainty	0.620	0.630	1

4.3.2.5 Healthcare Services

The hypothesised Healthcare Services scale consisted of three items, with item 32 having been removed due to a level of missing data >10%. On multi-trait analysis, the scale showed excellent item internal consistency with mean item intercorrelation of 0.606 (Table 4.14) and equal item-to-total correlation. The scale also showed good item

discriminant validity with all correlation values with other total scale scores being <0.4 (Table 4.5).

Table 4.14: Healthcare Services scale item intercorrelation matrix

	29. Information	30. Knowledge	31. Tests
29. Information	1	0.684	0.596
30. Knowledge	0.684	1	0.537
31. Tests	0.596	0.537	1

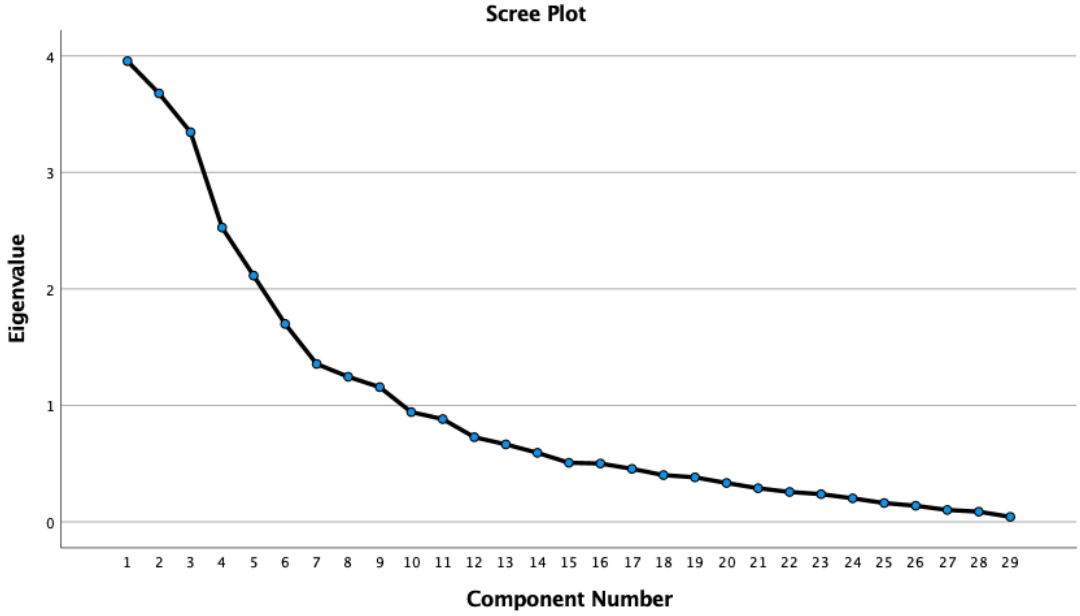
In summary, the multi-trait analysis of the LRRC-QoL failed to show unidimensionality across all of its hypothesised scales. The Healthcare Services and gender-specific Sexual Function scales demonstrated scale unidimensionality, meeting the criteria for item internal consistency and item discriminant validity. However, there were some concerns regarding the other scales; the Symptoms scale did not demonstrate item internal consistency. The Psychological Function and Future Perspective scales did not demonstrate item discriminant validity, indicating there may be some overlap within the concepts measured by these scales. In light of these findings, the decision was made to further test the scale structure of the LRRC-QoL through exploratory factor analysis (EFA).

4.3.3 Exploratory Factor Analysis

The first step in undertaking EFA was to establish the suitability of the dataset, this was done through calculating KMO and Bartlett's statistics. The KMO statistic for the 29 items included in the analysis was 0.611 and Bartlett's statistic was 1730 (df.=406, p=0.000). EFA was conducted to identify emerging factors representing correlations between items which may not have previously been hypothesised.

Eigenvalues indicate the substantive importance of that factor (or the degree of variation), therefore only eigenvalues >1.00 were retained. A scree plot is a graph of each eigenvalue against the factor it is associated with, illustrating the relative importance of each factor. Nine factors with an eigenvalue >1.00 were identified, as illustrated in the Scree plot (Figure 4.1), these factors accounted for 72.7% of the common variance.

Figure 4.1: Scree plot of extracted factors with Eigenvalue >1.00



The nine emerging factors identified through EFA (Table 4.15) were renamed to reflect their items:

Factor 1 – Sexual Function (gender specific)

Factor 2 – Psychological Impact

Factor 3 – Urostomy

Factor 4 – Pain and Dependence

Factor 5 – Healthcare Services

Factor 6 – Lower Limb Symptoms

Factor 7 – Stoma and Wound Issues

Factor 8 – Urinary Symptoms

Factor 9 – Sexual Interest

Table 4.15: Scales identified through Exploratory Factor Analysis

LRRC-QoL Item	Factor								
	1	2	3	4	5	6	7	8	9
5. Vaginal bleeding or discharge	-0.900	0.067	-0.002	0.044	0.014	0.057	0.099	-0.029	0.000
6. Vaginal irritation	-0.890	0.084	-0.085	0.143	-0.003	-0.022	0.086	-0.086	-0.020
24. Erectile function	0.853	0.025	-0.012	-0.006	0.127	0.077	0.098	0.023	0.106
25. Ejaculatory function	0.848	0.036	-0.032	0.066	-0.028	0.055	0.131	-0.117	0.126
27. Future treatments	-0.100	0.859	-0.041	-0.034	-0.022	-0.046	-0.035	-0.022	0.031
28. Uncertainty	0.056	0.830	-0.084	0.154	0.068	0.056	0.014	0.091	0.031
26. Results	-0.047	0.825	-0.037	0.041	-0.144	-0.060	0.055	-0.074	0.056
21. Attractiveness	0.016	0.563	0.058	0.149	0.083	-0.020	0.274	0.242	-0.182
14. Problems caring for urostomy	0.001	-0.064	0.948	0.014	0.032	0.062	0.088	-0.090	-0.074
16. Dependence on others for caring for urostomy	0.043	-0.079	0.913	0.008	-0.007	0.130	0.137	-0.104	-0.030
15. Embarrassment from urostomy	-0.008	0.012	0.905	0.021	0.139	-0.031	0.114	-0.056	-0.083
3. Perianal / buttock pain	0.048	0.088	0.057	0.785	-0.014	0.110	0.164	0.076	0.020
2. Back pain	-0.145	0.096	0.010	0.694	0.056	0.284	0.041	-0.026	0.081
4. Rectal bleeding or discharge	0.138	-0.051	0.024	0.600	-0.176	-0.163	-0.286	0.041	-0.148

1. Abdominal pain	-0.256	0.114	-0.070	0.596	0.090	0.058	0.090	0.255	-0.071
20. Dependence	-0.004	0.433	-0.008	0.482	0.040	0.302	-0.265	0.025	-0.049
29. Information	-0.066	0.028	0.053	0.044	0.872	0.001	0.032	-0.016	0.068
30. Knowledge	0.106	0.003	-0.007	0.075	0.824	-0.066	0.109	-0.150	0.030
31. Tests	0.064	-0.094	0.104	-0.093	0.815	0.046	0.019	0.010	-0.061
9. Lower limb weakness	0.010	0.002	0.073	0.113	-0.020	0.875	-0.034	0.088	-0.060
11. Lower limb numbness	0.037	-0.099	-0.027	-0.036	0.058	0.766	0.298	0.002	-0.098
10. Difficulty walking	0.087	0.060	0.151	0.393	-0.044	0.752	0.006	0.128	0.074
18. Embarrassment from stoma	-0.007	0.217	0.185	-0.035	0.167	0.041	0.792	-0.006	-0.151
19. Problems caring for stoma	0.002	-0.006	0.212	0.034	0.035	0.238	0.753	-0.189	-0.038
12. Pain/discharge from wounds	0.187	-0.212	-0.008	0.247	-0.357	-0.178	0.407	0.145	0.146
7. Urinary irritation	0.167	0.070	-0.114	0.071	-0.061	-0.002	-0.084	0.865	0.108
8. Urinary incontinence	-0.159	0.033	-0.141	0.175	-0.136	0.212	-0.053	0.706	-0.018
22. Pain during sexual intercourse	0.023	0.002	-0.056	0.118	0.067	-0.134	-0.110	0.109	0.872
23. Interest in sex	0.331	0.012	-0.164	-0.266	-0.060	0.051	-0.020	-0.037	0.727

Green shading indicates correlation values for items comprising the revised scales.

4.3.4 Multi-trait Scaling on Revised Scales

The nine revised scales identified through EFA were subjected to further testing through multi-trait analysis. This was undertaken to establish whether the revised scales showed unidimensionality in their proposed scale structure. The Healthcare Services scale was retained in its existing form. Table 4.16 lists the summary statistics for the revised scales. The multi-trait, multi-item correlation matrix for the revised scales is shown in Table 4.17.

Table 4.16: Item summary statistics for revised LRRC-QoL scales

Scale	No of Items	Mean Item Intercorrelation	Item Discriminant Validity (Range of Scores)	Item to Total Correlations
Female Sexual Function	2	0.899	-0.169 – 0.349	0.899
Male Sexual Function	2	0.775		0.775
Psychological Impact	4	0.497	-0.095 – 0.396	0.410 – 0.704
Urostomy	3	0.832	-0.212 – 0.314	0.834 – 0.917
Pain and Dependence	5	0.322	-0.245 – 0.481	0.328 – 0.549
Healthcare Services	3	0.606	-0.223 – 0.184	0.619 – 0.719
Lower Limb Symptoms	3	0.560	-0.122 – 0.328	0.557 – 0.696
Stoma and Wound Issues	3	0.267	-0.139 – 0.316	0.091 – 0.633
Urinary Symptoms	2	0.454	-0.223 – 0.259	0.454
Sexual Interest	2	0.476	-0.215 – 0.289	0.476

Table 4.17: Multi-trait/multi-item correlation matrix for the LRRC-QoL revised scales

	Scale								
	Sexual Function	Psychological Impact	Urostomy	Pain & Dependence	Healthcare Services	Lower Limb Symptoms	Stoma & Wound Issues	Urinary Symptoms	Sexual Interest
5. Vaginal bleeding or discharge	-0.366	0.096	0.012	0.094	-0.019	0.028	0.025	0.003	-0.223
6. Vaginal irritation	-0.363	0.122	-0.065	0.169	-0.046	-0.035	-0.021	-0.035	-0.234
24. Erectile function	0.869	-0.004	0.018	-0.043	0.121	0.111	0.097	0.004	0.275
25. Ejaculatory function	0.881	0.024	0.015	-0.005	0.016	0.117	0.109	-0.074	0.289
27. Future treatments	-0.026	0.847	-0.088	0.139	-0.026	-0.066	-0.002	0.034	0.003
28. Uncertainty	0.099	0.822	-0.111	0.310	0.028	0.058	0.070	0.188	0.006
26. Results	0.034	0.811	-0.072	0.156	-0.110	-0.046	0.083	0.057	0.011
21. Attractiveness	0.110	0.676	0.059	0.259	0.035	0.094	0.213	0.115	-0.114
14. Problems caring for urostomy	0.013	-0.087	0.964	0.006	0.108	0.139	0.266	-0.223	-0.215
16. Dependence due to urostomy	0.005	-0.092	0.930	-0.001	0.079	0.193	0.316	-0.220	-0.182
15. Embarrassment from urostomy	0.006	-0.010	0.932	0.022	0.184	0.067	0.265	-0.223	-0.186
3. Perianal / buttock pain	0.179	0.184	0.079	0.757	-0.026	0.291	0.166	0.179	-0.087
2. Back pain	-0.005	0.162	0.038	0.739	0.032	0.328	0.089	0.141	-0.101
4. Rectal bleeding or discharge	0.042	-0.003	-0.019	0.572	-0.143	-0.019	-0.128	0.190	-0.056
1. Abdominal pain	-0.086	0.200	-0.042	0.645	0.021	0.181	0.042	0.259	-0.158
20. Dependence	-0.040	0.396	-0.040	0.664	0.011	0.301	-0.058	0.171	-0.062
29. Information	0.099	0.040	0.110	0.015	0.878	0.029	0.031	-0.111	-0.007
30. Knowledge	0.120	0.025	0.080	-0.007	0.835	-0.036	0.091	-0.190	0.003
31. Tests	-0.002	-0.095	0.146	-0.077	0.858	0.039	0.085	-0.127	-0.031
9. Lower limb weakness	0.052	0.017	0.102	0.267	-0.006	0.863	0.069	0.178	-0.111

11. Lower limb numbness	0.164	-0.061	0.086	0.081	0.074	0.809	0.275	0.053	-0.090
10. Difficulty walking	0.165	0.087	0.157	0.481	-0.028	0.850	0.123	0.244	-0.021
18. Embarrassment from stoma	0.145	0.244	0.275	0.009	0.175	0.123	0.835	-0.119	-0.154
19. Problems caring for stoma	0.075	0.027	0.314	0.020	0.126	0.277	0.865	-0.154	-0.135
12. Pain/discharge from wounds	0.077	-0.089	0.005	0.074	-0.223	-0.016	0.418	0.127	0.051
7. Urinary irritation	0.096	0.120	-0.212	0.157	-0.124	0.069	-0.122	0.824	0.134
8. Urinary incontinence	-0.169	0.098	-0.192	0.294	-0.152	0.235	-0.045	0.879	-0.014
22. Pain during sexual intercourse	0.060	-0.005	-0.154	0.067	0.042	-0.122	-0.139	0.119	0.805
23. Interest in sex	0.349	-0.046	-0.196	-0.245	-0.053	-0.041	-0.094	0.008	0.905

Blue shading indicates results for item-to-scale correlation for the scale of interest, orange shading indicates values >0.4 for item discriminant validity.

4.3.4.1 Gender Specific Sexual Function

The revised Sexual Function scale consisted of two sets of gender-specific items. Overall, the scale demonstrates good item internal consistency; the female Sexual Function scale had a mean item intercorrelation of 0.899 (Table 4.18) and the male Sexual Function scale had a mean item intercorrelation of 0.775 (Table 4.19). Item-to-total correlation demonstrated equivalent correlations within the two sets of gender-specific items (Table 4.17). There was good item discriminant validity for the overall scale.

Table 4.18: Revised Female Sexual Function scale item intercorrelation matrix

	5. Vaginal bleeding or discharge	6. Vaginal irritation
5. Vaginal bleeding or discharge	1	0.899
6. Vaginal irritation	0.899	1

Table 4.19: Revised Male Sexual Function scale item intercorrelation matrix

	13. Erectile function	14. Ejaculatory function
15. Erectile function	1	0.775
25. Ejaculatory function	0.775	1

4.3.4.2 Psychological Impact

The revised Psychological Impact scale consisted of four items, the scale exhibited good item internal consistency with mean item intercorrelation of 0.497 (Table 4.20) and item-to-total correlation was >0.3 for all items. The revised scale also displayed good item discriminant validity.

Table 4.20: Psychological Impact scale item intercorrelation matrix

	16. Future treatments	17. Uncertainty	26. Results	21. Attractiveness
27. Future treatments	1	0.630	0.666	0.388
28. Uncertainty	0.630	1	0.620	0.357
26. Results	0.666	0.620	1	0.322
21. Attractiveness	0.388	0.357	0.322	1

4.3.4.3 Urostomy

The new Urostomy scale consisted of three items specific to patients with a urostomy. The scale demonstrated good item internal consistency with mean item intercorrelation of 0.832 (Table 4.21) and equal item-to-total correlation. The scale also showed good item discriminant validity with no correlations >0.4 with any of the other revised scales.

Table 4.21: Urostomy scale item intercorrelation matrix

	14. Problems caring for urostomy	16. Dependence on others for caring for urostomy	15. Embarrassment from urostomy
14. Problems caring for urostomy	1	0.883	0.845
16. Dependence on others for caring for urostomy	0.883	1	0.769
15. Embarrassment from urostomy	0.845	0.769	1

4.3.4.4 Pain and Dependence

The new Pain and Dependence Scale failed to demonstrate item intercorrelation for all values (Table 4.22). Items measuring pain demonstrated good item intercorrelation, however, there were no significant correlations between the other items, particularly item 20, suggesting it does not measure the same underlying concept as the other items within this revised scale. On assessing for item discriminant validity, item 10, which assesses

difficulty walking and is situated within the revised Lower Limb Symptoms scale, had a value of >0.4, suggesting an overlap in the constructs being measured (Table 4.17).

Table 4.22: Pain and Dependence scale item intercorrelation matrix

	3. Perianal / buttock pain	2. Back pain	4. Rectal bleeding or discharge	1. Abdominal pain	20. Dependence
3. Perianal/ buttock pain	1	0.484	0.327	0.397	0.291
2. Back pain	0.484	1	0.156	0.446	0.370
4. Rectal bleeding or discharge	0.327	0.156	1	0.175	0.289
1. Abdominal pain	0.397	0.446	0.175	1	0.286
20. Dependence	0.291	0.370	0.289	0.286	1

4.3.4.5 Healthcare Services

The Healthcare Services scale was unchanged from the initial multi-trait analysis. The scale showed good item discriminant validity when compared with the scales in the revised LRRC-QoL (Table 4.17).

4.3.4.6 Lower Limb Symptoms

The new Lower Limb Symptoms scale consisted of three items. The scale demonstrated good item internal consistency with mean item intercorrelation of 0.560 (Table 4.23) and equal item-to-total correlations. Item 10, which pertains to difficulty walking had a value of >0.4 correlation with the Pain and Dependence scale, suggesting an overlap in the constructs being measured and therefore demonstrating poor item discriminant validity (Table 4.17).

Table 4.23: Lower Limb Symptoms scale item intercorrelation matrix

	9. Lower limb weakness	11. Lower limb numbness	10. Difficulty walking
9. Lower limb weakness	1	0.537	0.663
11. Lower limb numbness	0.537	1	0.481
10. Difficulty walking	0.663	0.481	1

4.3.4.7 Stoma and Wound Issues

The new Stoma and Wound Issues scale, consisting of three items, with items 18-19 being specific to patients with a stoma. The scale failed to show good item internal consistency with only items 18 and 19 showing item intercorrelation (Table 4.24). All values showed item-to-total correlation of >0.3, however the correlation value for item 12 was lower than that for items 18 and 19. The scale also showed good item discriminant validity with no correlations >0.4 with any of the other revised scales.

Table 4.24: Stoma and Wound Issues scale item intercorrelation matrix

	18. Embarrassment from stoma	19. Problems caring for stoma	12. Pain/discharge from wounds
18. Embarrassment from stoma	1	0.616	-0.012
19. Problems caring for stoma	0.616	1	0.197
12. Pain/discharge from wounds	-0.012	0.197	1

4.3.4.8 Urinary Symptoms

The new Urinary Symptoms scale consisted of two items. The scale demonstrated good item internal consistency with mean item intercorrelation 0.454 (Table 4.25) and equal

item-to-total correlation. The scale also showed good item discriminant validity with no correlations >0.4 with any of the other revised scales.

Table 4.25: Urinary Symptoms scale item intercorrelation matrix

	7. Urinary irritation	8. Urinary incontinence
7. Urinary irritation	1	0.454
8. Urinary incontinence	0.454	1

4.3.4.9 Sexual Interest

The new Sexual Interest scale consisted of two items. The scale demonstrated good item internal consistency with mean item intercorrelation 0.476 (Table 4.26) and equal item-to-total correlation. The scale also showed good item discriminant validity.

Table 4.26: Sexual Interest scale item intercorrelation matrix

	22. Pain during sexual intercourse	23. Interest in sex
22. Pain during sexual intercourse	1	0.476
23. Interest in sex	0.476	1

4.3.4.10Multi-trait Scaling Analysis Summary of Revised Scales

The revised Sexual Function, Psychological Impact, Urostomy, Healthcare Services, Lower Limb Symptoms, Urinary Symptoms and Sexual Interest scales all showed both good item internal consistency and item discriminant validity and were therefore placed within the final scale structure for the LRRC-QoL.

The Pain and Dependence scale showed good item intercorrelation between items 1-3, however performed less well for items 4 and 20, indicating a lack of unidimensionality within the scale. The decision was therefore undertaken to remove items 4 and 20 and rename the scale as the Pain scale, repeat multi-trait analysis demonstrated good item internal consistency (Table 4.27).

Table 4.27: Revised Pain scale item intercorrelation matrix

	3. Perianal / buttock pain	2. Back pain	1. Abdominal pain
3. Perianal / buttock pain	1	0.484	0.397
2. Back pain	0.484	1	0.446
1. Abdominal pain	0.397	0.446	1

The Stoma and Wound Issues scale also failed to illustrate unidimensionality, with item 12 showing a lack of item intercorrelation with items 18 and 19. Item 12 was therefore removed, the scale was renamed as the Stoma scale and performed well on repeat multi-trait analysis. Items 4, 12 and 20 will be retained as individual items within the LRRC-QoL.

4.3.5 Scale Reliability

The LRRC-QoL demonstrated good reliability, with Cronbach's Alpha values of >0.7 for the majority of the revised scales. The ICC values were all >0.7 indicating that the scales showed good temporal stability (Table 4.28).

Table 4.28: Scale reliability

Scale	Cronbach's Alpha (95% Confidence Intervals)	ICC (95% Confidence Intervals)
Female Sexual Function	0.95 (0.92 – 0.96)	0.92 (0.89 – 0.94)
Male Sexual Function	0.87 (0.82 – 0.91)	0.84 (0.79 – 0.88)
Psychological Impact	0.79 (0.72 – 0.85)	0.85 (0.80 – 0.89)
Urostomy	0.93 (0.91 – 0.95)	0.88 (0.84 – 0.91)
Healthcare Services	0.81 (0.74– 0.86)	0.83 (0.77 – 0.87)
Lower Limb Symptoms	0.79 (0.71 – 0.85)	0.88 (0.84 – 0.91)
Urinary Symptoms	0.62 (0.45 – 0.74)	0.77 (0.69 – 0.83)
Sexual Interest	0.62 (0.45 – 0.74)	0.70 (0.60 – 0.78)
Stoma	0.75 (0.64 – 0.83)	0.88 (0.84 – 0.91)
Pain	0.70 (0.59 – 0.78)	0.81 (0.75 – 0.86)

4.3.6 Scale Validity

4.3.6.1 Construct Validity

The repeat multi-trait analysis following exploratory factor analysis has shown that the nine identified scales demonstrate unidimensionality and therefore construct validity.

4.3.6.2 Convergent Validity

Convergent validity was assessed using Pearson's Correlation Coefficient (r) to conduct correlational analysis comparing the scales of the LRRC-QoL to those for the EORTC QLQ-CR29 and FACT-C. Several a priori hypotheses were made in relation to convergent validity of the LRRC-QoL with the EORTC QLQ-CR29 and FACT-C:

- The LRRC-QoL Psychological Impact scale would correlate well with the EORTC QLQ-CR29 Body Image scale and the FACT-C Emotional Well-Being scale.

- The LRRC-QoL Pain scale would correlate well with the FACT-C Physical Well-Being scale.
- The LRRC-QoL Urinary Symptoms scale would correlate well with the EORTC QLQ-CR29 Urinary frequency scale.
- The LRRC-QoL Stoma scale would correlate well with the EORTC QLQ-CR29 Frequency of Bowel Movements scale.

The results of the convergent validity analysis are highlighted in Tables 4.29-4.30. The LRRC-QoL Pain scale demonstrated significant correlation (r >0.45) with the FACT-C Physical Well Being scale, r=0.538, (p=0.00). The LRRC-QoL Psychological Impact scale correlated well with the EORTC QLQ-CR29 Body Image scale, r=0.680, (p=0.00) and with the FACT-C Emotional Well-Being scale, r=0.326 (p=0.00). The LRRC-QoL Urinary Symptoms scale demonstrated moderate correlation with the EORTC QLQ-CR29 Urinary Frequency scale, r=0.310 (p=0.00). The LRRC-QoL Stoma scale did not correlate with the EORTC QLQ-CR29 Frequency of Bowel Movements scale, r=0.009 (p=0.00).

4.3.6.3 Known Groups Comparison

Demographic and clinical characteristics were used to identify groups of patients with the hypothesis that the LRRC-QoL would be able to distinguish between them. These groups were:

- Gender – male versus female,
- Pattern of recurrence – anterior, central, lateral, or posterior,
- Treatment intent – palliative versus curative,
- Presence of metastatic disease – metastatic disease versus no metastases,

- Pre-operative treatment for recurrence – no neoadjuvant treatment versus neoadjuvant treatment,
- Current disease status – disease free, distant disease recurrence or local disease recurrence.

Pre-operative treatments were combined due to small numbers within groups, with one patient receiving pre-operative chemotherapy, two patients receiving radiotherapy and 19 patients receiving chemoradiation. Only patients who responded to the items within the Urostomy and Stoma scales were included in the analysis for these scales. Overall, there were high rates of missing clinical data across most clinical categories of data included in the known groups comparison (excluding gender), ranging from 18.8% for treatment intent to 58.1% for pre-operative treatment for recurrence.

The LRRC-QoL found significant differences between several of the groups identified (Tables 4.31-4.33). The Psychological Impact scale was found to have significantly higher scores, indicating greater psychological impact, for patients with posterior recurrence and the Urinary Symptoms scale showed higher scores, indicating higher burden of symptoms, in patients with central disease. Female patients had significantly lower scores in the Sexual Interest and Sexual Function scales, indicating that female patients showed lower interest in sexual intercourse and reported fewer symptoms related to vaginal irritation, bleeding, or discharge. Patients undergoing curative treatment showed significantly higher scores, indicating worse Sexual Function. Finally, the Pain scale showed higher scores in patients with local disease re-recurrence compared with patients who were disease free or with distant disease recurrence.

Table 4.29: Convergent validity between the LRRC-QoL and EORTC QLQ-CR29 scales

EORTC QLQ-CR29 Scales		LRRC-QoL Scales								
		Psychological Impact Scale	Urostomy Issues	Lower Limb Symptoms	Urinary Symptoms	Sexual Interest	Sexual Function	Pain	Stoma	Healthcare Services
Urinary Frequency	r	-0.078	-0.164	0.101	0.310	-0.022	0.096	0.095	-0.088	0.189
	P value	0.474	0.128	0.350	0.004	0.839	0.375	0.384	0.419	0.079
	95% CI	-0.299-0.140	-0.414-0.053	-0.115-0.320	0.094-0.461	-0.216-0.176	-0.119-0.312	-0.131-0.337	-0.290-0.122	-0.021-0.377
Blood / Mucus in Stools	r	0.093	-0.253	-0.001	0.306	-0.006	-0.050	0.410	-0.093	-0.131
	P value	0.379	0.015	0.992	0.003	0.956	0.635	0.000	0.382	0.217
	95% CI	-0.120-0.312	-0.494--0.053	-0.227-0.225	0.093-0.446	-0.198-0.187	-0.260-0.160	0.233-0.645	-0.292-0.113	-0.334-0.077
Body Image	r	0.680	-0.034	0.073	0.192	-0.168	0.135	0.320	0.192	0.030
	P value	0.000	0.750	0.492	0.070	0.113	0.205	0.002	0.070	0.782
	95% CI	0.542-0.863	-0.267-0.193	-0.148-0.306	-0.014-0.353	-0.347-0.037	-0.075-0.346	0.128-0.557	-0.015-0.385	-0.177-0.234
Frequency of Bowel Movements	r	0.220	-0.113	-0.186	0.072	-0.128	0.068	0.007	0.009	-0.057
	P value	0.046	0.307	0.092	0.520	0.250	0.541	0.953	0.939	0.607
	95% CI	0.005-0.459	-0.366-0.117	-0.435-0.033	-0.108-0.212	-0.279-0.073	-0.154-0.292	-0.230-0.244	-0.202-0.218	-0.265-0.156

Green shading indicates the hypothesised correlations.

Table 4.30: Convergent validity between the LRRC-QoL and FACT-C scales

FACT-C		LRRC-QoL Scales								
		Psychological Impact Scale	Urostomy Issues	Lower Limb Symptoms	Urinary Symptoms	Sexual Interest	Sexual Function	Pain	Stoma	Healthcare Services
Physical Well Being	r	0.276	0.091	0.410	-0.023	-0.217	0.185	0.538	0.358	0.123
	P value	0.003	0.340	0.000	0.810	0.021	0.050	0.000	0.000	0.194
	95% CI	0.095 – 0.457	-0.097 – 0.278	0.239 – 0.582	-0.211 – 0.165	-0.401 - - 0.034	0.000 – 0.370	0.379 – 0.696	0.182 – 0.534	-0.064 – 0.310
Social Well Being	r	-0.121	0.237	0.184	-0.358	-0.159	0.130	-0.037	0.376	0.143
	P value	0.211	0.014	0.056	0.000	0.100	0.180	0.703	0.000	0.140
	95% CI	-0.307 – 0.068	0.049 – 0.423	-0.005 – 0.374	-0.542 - - 0.180	-0.354 – 0.032	-0.061 – 0.320	-0.227 – 0.153	0.198 – 0.555	-0.046 – 0.322
Emotional Well Being	r	0.326	0.169	0.054	-0.197	-0.126	0.129	0.108	0.303	-0.025
	P value	0.000	0.075	0.569	0.037	0.185	0.175	0.258	0.001	0.794
	95% CI	0.148 – 0.504	-0.017 – 0.350	-0.135 – 0.244	-0.384 - - 0.012	-0.315 – 0.061	-0.059 – 0.317	-0.080 – 0.297	0.123 – 0.484	-0.214 – 0.164
Functional Well Being	r	0.000	0.062	-0.085	-0.321	-0.050	0.228	-0.227	0.366	0.084
	P value	0.996	0.516	0.378	0.001	0.599	0.016	0.017	0.000	0.381
	95% CI	-0.192 – 0.191	-0.126 – 0.249	-0.275 – 0.105	-0.505 - - 0.142	-0.242 – 0.140	0.044 – 0.414	-0.415 - - 0.042	0.189 – 0.542	-0.106 – 0.274
Colorectal Scale	r	-0.010	0.230	0.087	-0.397	-0.098	0.159	-0.065	0.380	0.179
	P value	0.920	0.019	0.382	0.000	0.321	0.107	0.513	0.000	0.069

	95% CI	-0.205 – 0.185	0.037 – 0.397	-0.105 – 0.272	-0.594 - - 0.223	-0.299 – 0.099	-0.035 – 0.354	-0.265 – 0.133	0.201 – 0.567	-0.014 – 0.361

Table 4.31: Known groups comparison for the Psychological Impact, Urostomy Issues, and Lower Limb Symptoms scales

	Psychological Impact				**Urostomy Issues**				**Lower Limb Symptoms**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	81	8.6	2.7	0.214	19	4.5	1.4	0.914	81	5.6	2.4	0.953
Female	32	9.3	2.9		5	4.4	1.1		32	5.7	2.3	
Pattern of Recurrence												
Anterior	12	8.1	2.5	0.008	6	4.0	0.9	0.266	12	5.9	2.2	0.868
Central	24	9.5	2.6		2	4.5	0.7		24	6.0	2.4	
Lateral	27	7.9	2.6		3	3.3	0.6		27	5.7	2.5	
Posterior	20	10.4	2.8		5	4.8	1.3		20	5.4	2.2	
Presence of Metastatic Disease												
Yes	12	9.5	3.4	0.495	0	-	-	N/A	12	5.7	2.3	0.919
No	69	8.9	2.7		16	4.2	1.0		69	5.7	2.4	
Treatment Intent												

Palliative	21	9.0	3.4	0.832	0	-	-	N/A	21	5.1	1.3	0.038
Curative	70	8.8	2.5		19	4.3	1.3		70	6.0	2.6	
Pre-operative Treatment												
None	9	9.8	3.3	0.965	0	-	-	N/A	9	5.2	2.9	0.722
Yes	22	9.7	2.7		1	6.0	-		22	5.6	2.4	
Current Disease Status												
Disease free	41	9.1	2.7	0.104	12	4.2	0.9	0.114	41	5.6	2.6	0.221
Distant disease recurrence	4	12.0	2.2		1	6.0	-		4	4.5	0.6	
Local disease recurrence	13	8.8	2.7		1	3.0	-		13	6.7	2.2	

Green shading indicates statistically significant results.

Table 4.32: Known groups comparison for the Urinary Symptoms, Sexual Interest, and Sexual Function scales

	Urinary Symptoms				**Sexual Interest**				**Sexual Function**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	81	2.9	1.3	0.788	81	3.2	1.4	0.006	81	5.0	2.1	0.000
Female	32	3.0	1.1		32	2.5	1.0		32	2.3	1.0	
Pattern of Recurrence												
Anterior	12	2.8	1.0	0.024	12	2.5	0.6	0.401	12	4.7	2.3	0.797
Central	24	3.7	1.6		24	3.2	1.6		24	4.1	2.2	
Lateral	27	2.6	0.7		27	2.8	1.2		27	4.1	2.5	
Posterior	20	3.2	1.5		20	3.1	1.4		20	3.8	2.2	
Presence of Metastatic Disease												
Yes	12	2.8	1.0	0.506	12	3.2	2.1	0.504	12	3.5	1.9	0.324
No	69	3.1	1.4		69	2.9	1.2		69	4.2	2.4	
Treatment Intent												

Palliative	21	3.3	1.8	0.397	21	2.9	1.6	0.960	21	3.1	1.3	0.004
Curative	70	3.0	1.2		70	2.9	1.2		70	4.3	2.4	
Pre-operative Treatment												
None	9	3.1	1.1	0.740	9	3.1	1.6	0.789	9	6.1	3.0	0.105
Yes	22	3.3	1.3		22	3.0	1.1		22	4.5	2.2	
Current Disease Status												
Disease free	41	2.9	1.1	0.131	41	3.0	1.3	0.769	41	4.5	2.5	0.552
Distant disease recurrence	4	2.8	1.0		4	2.7	1.0		4	4.1	1.2	
Local disease recurrence	13	3.7	1.8		13	2.8	1.0		13	3.6	2.4	

Table 4.33: Known groups comparison for the Pain, Stoma, and Healthcare Services scales

	Pain				**Stoma**				**Healthcare Services**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	81	5.1	1.8	0.124	47	3.0	1.0	0.292	81	9.8	2.2	0.845
Female	32	5.8	2.2		17	3.4	1.4		32	9.7	2.3	
Pattern of Recurrence												
Anterior	12	5.2	1.7	0.175	8	2.6	0.7	0.564	12	9.2	2.7	0.293
Central	24	6.0	2.7		13	3.4	1.4		24	10.5	1.5	
Lateral	27	4.8	1.5		13	3.1	1.1		27	9.4	2.3	
Posterior	20	5.2	1.4		11	3.1	1.2		20	10.0	2.7	
Presence of Metastatic Disease												
Yes	12	5.1	2.0	0.671	4	2.8	1.0	0.550	12	9.6	2.0	0.694
No	69	5.3	2.0		40	3.1	1.2		69	9.9	2.4	
Treatment Intent												

Palliative	21	5.2	2.0	0.982	5	3.2	1.3	0.899	21	9.3	2.0	0.262
Curative	70	5.2	1.9		46	3.1	1.1		70	10.0	2.3	
Pre-operative Treatment												
None	9	5.2	2.3	0.710	7	2.7	0.8	0.220	9	10.1	1.5	0.891
Yes	22	5.5	2.1		16	3.5	1.5		22	10.0	2.1	
Current Disease Status												
Disease free	41	5.0	1.9	0.032	26	3.2	1.3	0.807	41	10.0	2.3	0.720
Distant disease recurrence	4	4.0	0.8		1	4.0	-		4	9.3	2.8	
Local disease re-recurrence	13	6.4	1.9		8	3.3	1.3		13	9.5	2.1	

4.4 Discussion

This chapter describes the psychometric analysis of the LRRC-QoL in a combined cohort of 117 patients recruited from the UK and Australia, using the same methodological approach previously described in the UK cohort alone (108). The resulting LRRC-QoL measure (see Appendix 3), consisting of 29 items in nine scales and three individual items, is a disease-specific measure of HrQoL in LRRC with a robust scale-structure, excellent reliability and good convergent and known groups validity.

The differences in the clinical characteristics of the patients recruited from the UK and Australia are likely to reflect the differences in the care pathways between the two countries. The increasingly specialist nature of the management of LRRC has led to the establishment of specialist referral pathways for centres treating patients with LRRC in many countries. In Australia, there is a national policy for referral pathways for pelvic exenteration services (12). Whereas in the UK, pelvic exenteration services are not formally centralised (11, 282). The higher proportion of patients undergoing curative surgery in the Australian cohort may reflect the nature of this national referral pathway to a highly specialist quaternary centre (283).

A thorough and systematic approach was applied to confirm the scale structure of the LRRC-QoL using both multi-trait analysis and exploratory factor analysis (EFA). Notably, the Symptoms scale failed to demonstrate unidimensionality, likely due to the varied range of symptoms addressed through this scale. The Psychological and Future Perspectives scales also showed significant overlap. As a result, EFA was undertaken to further test the scale structure of the LRRC-QoL, identifying eight new scales and

retaining the Healthcare Services scale. Notably, the revised scales divided the hypothesised Symptoms Scale into smaller scales consisting of groups of related symptoms and combined the Psychological and Future Perspective scales. Following this robust testing process, the final nine scales within the LRRC-QoL all demonstrated unidimensionality on repeat multi-trait analysis: confirming the construct validity of the measure. The LRRC-QoL demonstrated excellent reliability and temporal stability across all nine scales. It also exhibited good convergent validity, confirming the majority of hypotheses in relation to predicted correlations between the LRRC-QoL scales and those of the EORTC QLQ-CR29 and FACT-C measures.

The known groups comparison analysis demonstrated the ability of the LRRC-QoL to discriminate between scores in some clinically relevant patient groups. Scores for the Sexual Interest scale were higher in male patients, indicating higher levels of sexual interest. There is extensive research examining gender differences in sexuality and sexual behaviours, suggesting that men may display higher levels of sexual interest and libido, though these gender differences seem to be decreasing over time (284). The reasons for these differences are likely due to complex clinical, psychosocial, and cultural factors, one potential explanation for the differences in Sexual Interest scores is that female patients may experience greater levels of stigma attached to female sexuality leading to underreporting (284). It is worth noting that a higher proportion of female patients did not respond to the questions in the Sexual Interest scale (42.4% for question 22 and 27.3% for question 23) in comparison to male patients (28.6% for question 22 and 19.0% for question 23). Scores for Sexual Function were higher in patients undergoing curative treatment, this effect is likely due to the impact of surgery and its associated morbidity on sexual function (176). Scores were also higher in male patients, indicating poorer

function; erectile dysfunction is a well-recognised and common consequence of treatment including pelvic radiotherapy and surgery (176, 285, 286).

Scores for the Urinary Symptoms scale were higher in patients with central and posterior disease, indicating worse function. The bladder is supplied by sympathetic nerves which arise from the hypogastric plexuses, parasympathetic nerves arising from the pelvic splanchnic nerves and the pudendal nerve which arises from the S2-S4 level of the spinal cord. Posterior disease involving the sacrum may invade the S2-S4 nerve roots leading to a higher incidence of urinary symptoms (100). Patients with central disease are likely to experience bladder involvement requiring surgery in the form of either total pelvic exenteration or urinary reconstruction including ureteric resection and Boari flap. Patients who have undergone urinary reconstruction are likely to experience a greater incidence of urinary symptoms (97). Scores were also higher for the Psychological Impact scale in patients with central and posterior disease. Patients with central disease are more likely to require a total pelvic exenteration to achieve complete excision of their disease, requiring two stomas in the form of a urostomy and colostomy. The presence of two stomas has been shown to impact upon body image which is a component of the Psychological Impact scale (287). Patients with posterior disease are more likely to require sacrectomy and patients undergoing sacrectomy, particularly high sacrectomy, have reported worse overall HrQoL, physical function and Short Form 36 (SF-36v2) mental component score (100).

Finally, scores for the Pain scale were higher in patients with local disease re-recurrence, this is unsurprising given that pain is a common symptom associated with local recurrence (164, 169, 182). The results for the known groups comparison overall demonstrate the

ability of the LRRC-QoL to discriminate between some clinically relevant groups, these results may be affected by the high rates of missing clinical data of up to 58.1% in the categories included in this analysis. Repeated assessment in an independent cohort of patients is likely to be of benefit in confirming the psychometric properties of the LRRC-QoL.

Recruiting patients with advanced malignancy is undoubtedly challenging, particularly for patients receiving palliative treatment; existing evidence regarding HrQoL in patients receiving palliative treatment for LRRC is limited though suggests that this group experience poor HrQoL (39). Smith et al. report a retrospective cohort of 30 patients receiving SABR re-irradiation, demonstrating an improvement in HrQoL measured by the EQ-VAS at 3-months following treatment (168). You et al. describe one of the only studies comparing HrQoL outcomes between patients receiving curative surgery, non-curative surgery, and non-operative treatment for LRRC (164). Their study includes one of the largest reported palliative cohorts with 43 patients receiving palliative treatments: including 13 patients undergoing non-curative surgery and 30 patients receiving non-operative treatment. Their results show that patients receiving palliative treatment reported worse scores in the FACT-C Physical Wellbeing scale over time when compared with patients undergoing curative surgery (164). Quyn et al.'s study reporting HrQoL outcomes in 21 patients undergoing palliative pelvic exenteration for both primary and recurrent pelvic malignancy reported that overall HrQoL was low at baseline and does not return to baseline post-operatively; contrary to the evidence reported in patients receiving curative treatment (101). The small cohort of 21 patients receiving palliative treatment in the psychometric analysis of the LRRC-QoL is an overall limitation of the study with only a significant difference in scores for Sexual Function demonstrated between patients receiving palliative and curative treatment. However, given the wider

context and challenges of recruiting this patient group, their inclusion remains an accomplishment. Future work will aim to build on recruiting a larger cohort of palliative patients to enable comparison in disease-specific HrQoL outcomes based on treatment intent.

A major strength of this study is the multi-centric, international nature of its recruitment strategy, including leading centres in the management of LRRC and signifies that the results reported are likely to be generalisable to other centres treating patients with LRRC internationally. The value of international, multi-centre collaboration has been illustrated through the work of the PelvEx collaborative; pooling international outcomes and experience to accrue greater understanding of the clinical outcomes following pelvic exenteration, including patients with LRRC (35). Applying this same international and collaborative approach on a larger scale is likely to be of great benefit in increasing potential recruitment to future studies reporting HrQoL in LRRC. Further use of the LRRC-QoL on an international platform requires a process of cross-cultural adaptation of the LRRC-QoL to enable its use in a greater number of both English-speaking and non-English-speaking countries. This process represents an important area of future work in the ongoing and evolving development of the LRRC-QoL and is described in chapter 5.

4.5 Conclusion

The recruitment of a cohort of 117 patients represents one of the largest studies of HrQoL in LRRC to date (97, 98, 104) and is a significant achievement in a challenging setting given the advanced and complex nature of this disease. Cross-cultural adaptation and further collaboration with international centres will allow for confirmation of the

generalisability, reliability, and validity of this measure in an external sample of patients through conducting a prospective, longitudinal cohort study to measure HrQoL at regular intervals. This will also allow for testing of the responsiveness of the LRRC-QoL, meaning its ability to measure changes over time. Establishing the responsiveness of the measure is an important development as it will enable the evaluation of the impact of LRRC and its treatments on HrQoL. These psychometric properties are evaluated in the external validation of the LRRC-QoL described in chapter 6.

Chapter 5 Cross-Cultural Adaptation of the Locally Recurrent Rectal Cancer – Quality of Life (LRRC-QoL) Questionnaire

5.1 Introduction

Cross-cultural adaptation is a process through which PROMs are adapted or translated for use in different cultures. The aim of cross-cultural adaptation is to produce measures that are conceptually, linguistically, and semantically congruent for use internationally (110). This process is an essential step in the development of a PROM to enable its use in a greater number of patients across many countries in both clinical and academic settings (113). Cross-cultural adaptation of the LRRC-QoL will expand the utility of the measure on an international platform, facilitating international, multi-centre collaboration to report disease-specific HrQoL in LRRC. It will also enable a greater number of patients to experience the potential benefits of incorporating the LRRC-QoL into routine clinical practice, such as monitoring individual response to treatment. The aim of this study was to translate the LRRC-QoL questionnaire into several different languages and to confirm the content validity and acceptability of the questionnaire within these cultures using cognitive interviews with patients who have been treated for LRRC within the last 2 years.

5.2 Methods

5.2.1 Translatability Assessment

Translatability assessment is "*the evaluation of the extent to which a PROM can be meaningfully translated into another language*" (288), with a meaningful translation of a PROM being one that is conceptually equivalent to the original and appropriate for use in the target country or culture (289). Translatability assessment involves a process of reviewing a PROM, defining its concepts, analysing the translatability of each part, describing any proposed changes, discussion with the original PROM developers, and preparing a report outlining this process and results (289).

5.2.1.1 Translatability Assessment in English-speaking Countries

Translatability assessments of the LRRC-QoL were undertaken to ensure that the questionnaire was conceptually equivalent for use in English-speaking countries outside of the UK and Australia. A single version of the questionnaire was agreed for use in all English-speaking countries in accordance with EORTC guidance (110). Healthcare professionals with expertise in treating patients with LRRC from participating sites in Ireland, the United States of America (USA), Canada, and New Zealand were consulted for translatability assessments. The questionnaire was sent to these teams for review and virtual interviews with healthcare professionals were undertaken to review and discuss each item of the questionnaire in turn with the researcher. This process aimed to clarify the concepts represented by each item, considering whether the concepts are appropriately reflected and phrased using appropriate terminology, considering the cultural context. Feedback from participating healthcare professionals was recorded and reviewed with the original developers of the questionnaire.

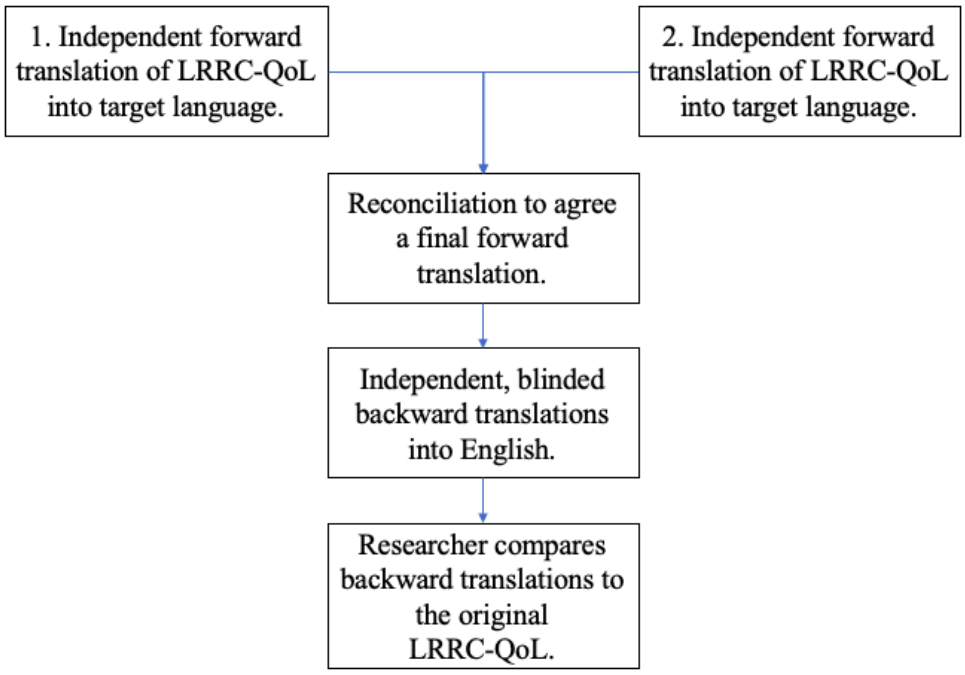
5.2.1.2 Translatability Assessment in Non-English-Speaking Countries

The LRRC-QoL was sent to all clinicians who would be involved in the translation process of the PROM for use in Brazil, Denmark, France, India, Italy, the Netherlands, Pakistan, Russia, Singapore, Spain, and Sweden. The participating clinicians were asked to review the items and highlight any issues from a linguistic or cultural perspective. Virtual meetings were then held to discuss the questionnaire to ensure the items and scales reflected the concept of interest appropriately. Feedback from the participating healthcare professionals was recorded and reviewed with the original developers of the questionnaire.

5.2.2 Translation of the LRRC-QoL

In accordance with EORTC guidance (110), a Forward-Backward approach was undertaken to translate the LRRC-QoL and is summarised in Figure 5.1. Forward translation was undertaken by two healthcare professionals with background knowledge of LRRC and who were native speakers of the target language: each preparing an independent translation of the questionnaire. These two translations were reviewed and compared to agree a final forward translation of the questionnaire. Backward translation of the questionnaire into English was then undertaken by professional translators who were blinded to the original English version. The backwards translations were compared to the original English LRRC-QoL to ensure consistency between the two. Any differences between the backwards translation and the original LRRC-QoL were discussed between the healthcare professionals who performed the forwards translation and the original developers of the LRRC-QoL.

Figure 5.1: Summary of the translation process



5.2.3 Pre-testing of the LRRC-QoL

Following translatability assessment and translation of the questionnaire, pre-testing was undertaken through cognitive interviews, with a sample size of 5-10 patients per version of the questionnaire. The aims of this interview were to determine the relevance of each item to the patients' experience of LRRC, to assess the comprehensiveness and the comprehensibility of the LRRC-QoL, and to confirm content validity, face validity, and acceptability of the LRRC-QoL (113). In countries where recruiting 5-10 patients with LRRC presented a significant challenge due to the rarity of LRRC, interviews with healthcare professionals were also undertaken, in keeping with the ISPOR task force report regarding PROs in rare diseases (290).

Ethical approval was gained in the UK for the study overall (REC reference: 20/WS/0116) and at each participating country and site in accordance with local

procedures. Participants were asked to provide informed, written consent prior to participating in the study.

The eligibility criteria for recruiting patients for cognitive interviews were:

- aged over or equal to 18 years,
- with radiological and/or histological diagnosis of LRRC,
- **or** have undergone treatment (surgery/chemotherapy/radiotherapy) for LRRC within the last **2 years,**
- able to provide informed written consent to participate **and**,
- able to read and write in the target language.

5.2.3.1 Data Collection

Prior to participating in the cognitive interview, participants were asked to complete the following:

- LRRC-QoL questionnaire,
- FACT-C questionnaire,
- EORTC QLQ-C30 questionnaire,
- EORTC QLQ-CR29 questionnaire,
- Demographics form:
    - Age,
    - Gender,
    - Ethnicity,
    - Marital status,
    - Education status,

- Employment status.

This data was collected either in person immediately before the interview, sent to the participant via post to complete and return prior to the interview, or sent to the participant via email to complete via REDCap. At some sites, including those in India, Pakistan, and Singapore, the interviewer completed the questionnaires through reading the questions to the participant, this a recognised and acceptable approach to administering PROMs (291). Data collected through administration of these questionnaires were included in the psychometric analysis described in chapter 6. At the time of recruitment, there was no validated Urdu version of the FACT-C, and no validated Hindi, Marathi, or Telugu version of the EORTC-CR29, therefore it was not possible to use these questionnaires in the validation of the LRRC-QoL.

5.2.3.2 Interview Procedure

Interviews with patients were undertaken either in person, via telephone, or via video-conference software using an interview guide (see Appendix 4), which was informed by the EORTC Translation manual (110). The interview included 6 questions which were posed in turn for each scale or set of questions in the questionnaire, this was undertaken pragmatically by scale rather than for each item in turn as it was felt that this approach would reduce the burden of the interview for participants and would be adequate to satisfy the objectives of the interview.

The questions for each scale/set of questions were as follows:

1. Is this experience relevant to your disease or treatment?
2. Were any of these questions difficult to answer?

3. Were any of these questions confusing?
4. Were any of these questions difficult to understand?
5. Were any of these questions upsetting or offensive?
6. If there are any comments regarding a question, ask the participant:
    a. How would you ask this question in your own words?

Questions were then posed in relation to the whole questionnaire, the first question being "Were there any questions that you found to be irrelevant?" followed by completing the QQ-10 measure with the participant. The QQ-10 is a 10-item questionnaire which was designed as a measure of face validity and acceptability of PROMs (292).

Participants in English-speaking countries were able to complete the questionnaires online using a REDCap form designed specifically for this purpose, a series of questions were also included for patients who had used this platform, these questions were:

1. Was the electronic platform easy to use?
2. Was the electronic platform easy to navigate?
3. Were the instructions difficult to understand?
4. Are there any ways in which the electronic platform could be improved?

The same facilitator performed all interviews with English-speaking patients to ensure consistency. Interviews with participants at non-English-speaking sites were facilitated by researchers based at the site who are native speakers of the target language. To ensure consistency in the approach used to the interviews, a detailed topic guide was used (see Appendix 4) and all facilitators participated in a virtual training meeting with the researcher prior to commencing the interviews.

Interviews with clinicians were undertaken remotely via video-conference software guided by the topic guide developed for use in patients. The questionnaires and QQ-10 were not administered to healthcare professionals.

5.2.4 Analysis of Interview Responses

Comments made by participants during the interview were recorded using a form designed for this purpose (see Appendix 4). Interview transcripts and feedback forms were reviewed to identify any comments regarding words, phrases, or expressions that were difficult to understand, unacceptable, or offensive. These comments were placed in a table listing feedback on an item-to-item basis and were reviewed in turn by the original developers of the LRRC-QoL.

Responses to the QQ-10 measure were scored as described by Moores et al. (292). The first six questions comprised the Value score, answers from strongly disagree to strongly agree were coded as 0-4 on a 5-point Likert scale. The final four questions comprised the Burden score. The scores for Value and Burden were then transformed onto a scale of 0-100. Using the QQ-10 to confirm face validity and acceptability requires a high mean Value score (over 70) and a low mean Burden score (under 25). Face validity is the degree to which a PROM appears to be an adequate reflection of the construct of interest (95).

5.3 Results

5.3.1 Translatability Assessment

5.3.1.1 Translatability Assessment in English-Speaking Countries

Review of the LRRC-QoL and interviews with clinicians from the USA, New Zealand, and Ireland resulted in the suggested changes to the measure displayed in Table 5.1. The suggested changes regarding the layout of the questionnaire were considered by the original questionnaire developers and following this were implemented for all versions of the questionnaire. These changes included placing the Stoma scale prior to the Urostomy scale, placing the Sexual Interest scale prior to the Sexual Function scale, and re-ordering the items within the Sexual Interest scale; placing the item "Have you been interested in sex?" before the item related to pain during sexual activity.

The content validity of the LRRC-QoL has been extensively tested in the UK and Australia and the wording of the LRRC-QoL had been found to be acceptable to this cohort of patients (108). Therefore, it was felt that changes to the wording of the LRRC-QoL, including to terms such as "dry ejaculation" and "urine bag", should only be undertaken with feedback from patients. Following this process, a final universal English-language version of the questionnaire to be pre-tested in the USA, New Zealand, Canada, and Ireland was confirmed.

Table 5.1: Feedback regarding the LRRC-QoL – English-speaking sites

Aspect of the Questionnaire	Suggested Change	Change Implemented?
Stoma scale	Move Stoma scale to be before Urostomy scale.	Yes

Stoma scale	Change "Have you felt embarrassed because of your stoma?" to "Have you felt embarrassed about your stoma?".	No
Urostomy scale	Change "urostomy (urine bag)" to "stoma bag for urine".	No
Urostomy scale	Remove "urinary catheter" as this is not the same as a Urostomy.	No, alternative amendment made (see table 2)
Sexual Interest scale	Move Sexual Interest scale to before Sexual Function scale.	Yes
Sexual Interest scale	Move "Have you been interested in sex?" to before "Have you had pain during sexual activity?".	Yes
Sexual Function scale	Clarify meaning of "dry ejaculation".	No
Sexual Function scale	Remove repetition of women/men in gender specific questions.	Yes

5.3.1.2 Translatability Assessment in Non-English-Speaking Countries

The LRRC-QoL was translated into Danish, Dutch, French, Hindi, Italian, Mandarin, Marathi, Portuguese, Russian, Spanish, Swedish, Telugu, and Urdu via the Forward-Backward translation process demonstrated in Figure 5.1. Translatability assessment identified several issues, particularly from a cultural perspective (see Table 5.2). Clinicians in Singapore felt that the questions related to sexual interest and function may not be tolerated from a cultural perspective. Following further discussion between the participating team in Singapore and the original developers of the LRRC-QoL, these scales were felt to represent important HrQoL issues relevant to patients with LRRC and were therefore not removed for the Mandarin version of the questionnaire. Clinicians in India felt that the reading level required to complete the questionnaire would be a barrier for some patients, it was agreed that the LRRC-QoL could be administered by the clinician reading aloud, which is recognised as equivalent to other modes of administration (291).

Participating clinicians involved in the translation process contributed additional feedback and suggested changes to the questionnaire (see Table 5.2). Following discussion with the original developers of the LRRC-QoL, changes were implemented for all language versions of the LRRC-QoL. These changes included the addition of an "Other Symptoms" heading above the individual items 9 and 10 and additional text to prompt the patient to skip question 9 should they no longer have a rectum or anus in situ; "Do you still have a rectum or anus? Yes, please answer question 9. No, please go to question 10."

Question 14, a skip question to give the option to complete items regarding a urostomy, was altered to reflect the items within the measure which reference the presence of a urinary catheter or nephrostomy. Therefore, the question was amended from "Do you have a urostomy (urine bag)?" to "Do you have a urostomy (urine bag), nephrostomy or urinary catheter?". This change was also implemented for all language versions of the measure.

Other suggested changes were not implemented following discussion with the original developers of the LRRC-QoL. A suggestion to change the time frame for items to be consistent throughout the measure was not implemented, given that the different timescales featured in the questionnaire were a direct result of feedback from patients during the development of the LRRC-QoL (108). The original questionnaire developers felt the addition of a "not applicable" answer was not necessary given that participants could circle "not at all" if a question is not relevant to them. Following further discussion, additional text above question 9 was added to prompt the patient to skip the question if not applicable to them.

Though the original developers agreed that the addition of an item regarding female sexual function and particularly female orgasm may be a relevant quality of life theme for patients with LRRC, they concluded that an item should not be added to the questionnaire without direct input from patients. Female orgasm was not identified during previous qualitative work to develop the LRRC-QoL (106), though it is possible that its omission was due to the personal nature of this experience and a reluctance from participants to discuss it, opposed to it lacking relevance.

Table 5.2: Feedback regarding the LRRC-QoL – non-English-speaking sites

Aspect of the Questionnaire	**Suggested Change**	**Change Implemented?**
General feedback	Suggest using same time frame for all questions.	No
General feedback	Reading level felt to be too high for some patients.	Yes, can be administered by clinician reading aloud.
Individual Items, questions 9 and 10	Addition of a heading, suggested "other symptoms".	Yes
Question 9	Addition of a "not applicable" answer for patients who do not have an anus following surgery.	No, alternative amendment made.
Question 10	Addition of a "not applicable" answer for patients who have not undergone surgery and therefore have no wound(s) or scar(s).	No
Urostomy scale, question 14	Suggest adding "urinary catheter" and "nephrostomy" to text of question 14 so that patients do not skip the scale if they have these but not a urostomy.	Yes
Sexual Interest and Sexual Function scales	Scales felt to be culturally insensitive.	No
Sexual Function scale, Female	Addition of a question regarding female orgasm.	No
Question 20	This appears as two questions in one, perhaps could be rephrased.	No

5.3.2 Pre-Testing of the LRRC-QoL

Following translation and review of the questionnaire by clinicians at English-speaking sites outside of the UK and Australia, pre-testing was undertaken through cognitive interviews with patients from each participating country. Pre-testing for the translated versions was undertaken in Brazil, Denmark, France, India, Italy, the Netherlands, Pakistan, Singapore, Spain, and Sweden. Thirteen sites in 12 countries participated in pre-testing of the questionnaire overall, including New Zealand and Canada, for the English version of the questionnaire.

5.3.2.1 Participant Demographics

Participant characteristics are detailed in full in chapter 6 due to their inclusion in the external validation of the LRRC-QoL. Sixty-seven patients were recruited to the cross-cultural adaptation study in total, an additional patient was recruited from Singapore, however, they withdrew from the study as they were offended by questions relating to sexual function. In relation to the patients included, 43 (64.2%) were male, median age was 64.0 (IQR 12.0), the majority (n=42, 62.7%) were of white ethnicity. The majority of patients (n=42, 62.7%) had undergone an Anterior Resection for PRC, the median interval between PRC and LRRC was 17.00 months (IQR 23.50), and for most patients (n=48, 71.6%) their recurrence was detected via surveillance. The majority of patients (n=57, 85.1%) included in the study were treated curatively. Five additional interviews were undertaken with healthcare professionals (HCPs) working in the countries where recruitment was challenging, including two in Spain, one in Singapore, and two in Canada.

5.3.2.2 Interview Responses

Comments from participants regarding items and scales in the LRRC-QoL and the decisions made in relation to changing the questionnaire are described in Table 5.3.

Table 5.3: Interview responses and resultant changes to the LRRC-QoL

Item	Participant number	Comments	Decision regarding item or scale
Whole Questionnaire			
Electronic PROMs	New Zealand 4 and 7	The participant stated that once the questionnaire has been completed, it disappears. "*Very easy to use, no problems at all*"	Investigate an option to review answers prior to submission using REDCap.
Positive feedback	Spanish 2	Important symptoms, problems, or concerns are all reflected. No areas or problems were especially over-represented.	No change.
	Dutch 1	Short and clear, no missing questions. Specific to my situation, clear overview.	No change.
	Canada 1	The patient felt that the questionnaire was "*well crafted*" and "*like it was tailored to me*".	No change.
Formatting	Dutch 3	Make questions 11 and 14 bold font.	Change implemented.
Instructions or timings	Spanish HCP 1	The first sentence on the front page is overly long and complicated, suggest changing to "*This questionnaire asks your point of view on your quality of life*."	No change, consistent across all questionnaires and not identified as an issue by patients.
	Danish 6	The patient felt there was no way of sharing other diagnoses which would be relevant, such as their previous knee surgery.	See Table 5.4.
	Swedish 1	The participant would like to have space to give more information about the reason they experience weakness in their leg.	No change, response options are in keeping with EORTC modules.
	Swedish 4	Suggested highlighting instructions related to timing: week/month, and gender: women/man, to help patients with identifying and answering questions that apply to them.	No change, no other patients suggested this change.
	New Zealand 5	The patient felt that the options for the answers were not descriptive enough. They suggested adding space for free text to add thoughts and feelings.	No change, response options are in keeping with EORTC modules.

Issues not represented	Spanish HCP 1	No questions related to losing work or the financial impact of LRRC and its treatment.	See Table 5.4.
	Italian 4	Symptoms related to defecation should be better explored: incontinence, diarrhoea etc.	See Table 5.4.
	Italian 10	"*Should ask about the psychological impact of ostomy*"	See Table 5.4.
	Dutch 10	Suggested adding questions about tiredness, appetite, loss of taste. Found sexual function questions to be irrelevant.	See Table 5.4.
	Swedish 1	The participant felt that there were no questions within the Psychological Impact scale regarding feeling sentimental or more vulnerable following surgery.	See Table 5.4.
	Swedish 3	The participant felt that the question did not include problems related to the placement of their stoma and urostomy, as theirs are placed close to each other. They also felt that there was a lack of questions regarding the postoperative course.	See Table 5.4.
	Swedish 4	The participant felt that the questionnaire lacked questions about work, time-off work, physical activity, and questions about metastases.	See Table 5.4.
	Swedish 7	The participant would like questions about complications after surgery to be included, for example foot and leg problems, urethral injury etc. The participant would like to add a question about if you feel that you were sufficiently informed about possible complications before surgery	See Table 5.4.
	Swedish 8	The participant felt there was a lack of questions about rehabilitation.	See Table 5.4.
	New Zealand 5	The patient suggested adding questions related to financial impact and counselling prior to surgery.	See Table 5.4.
	New Zealand 6	The participant felt that the following issues were missing from the questionnaire: lack of energy, tiredness and poor memory.	See Table 5.4.
	Canada 1	The patient stated that they find paying for their stoma supplies upfront expensive, though they are able to claim 80% of this expense through their health insurance.	See Table 5.4.

	Canada 2	The patient felt that a more general question should be included, "*How are you doing right now*?".	See Table 5.4.
Pain Scale			
1. Have you had abdominal pain?	Dutch 6	The patient suggested to please distinguish abdominal pain in "lower abdominal pain", "bowel complaints" and "pain in the pelvic area". This would translate to "*pijn in de onderbuik*", "*maag- en darmklachten*" and "*pijn in het kleine bekken*" respectively.	No change, discussed with clinical team and not felt to be required.
	Danish 2	The patient felt the term *"abdominal pain*" was unspecific.	No change, the clinical term felt this term was clear and no other patients shared this concern.
	New Zealand 5	The patient explained that they only experience pain upon lying down, they suggested adding a question to clarify, *"Is there a time or a certain position that causes you to experience pain?"* used the examples of during sleep, standing, pain on walking or bending over. And the additional question of *"Can you mitigate the pain?".*	No change, this was not felt to relate to a specific issue or concept.
2. Have you had pain in your lower back and/or pelvis?	Spanish HCP 1	Suggested changing "*en su zona lumbar*" to "*en la zona lumbar*" in question 2.	No change, not identified as an issue during forward-backward translation or patient interviews.
	Dutch 7	Not relevant for patient and did not know the term "*kleine bekken*". Location could be added "*skintje*" skin.	Term "*kleine bekken*" changed to "*bekkenregio*".
	Danish 5	Question 2 could be separated into a question for the lower back and a question for the pelvis.	See Table 5.4.
Overall scale	Danish 1	Felt that the time frame was too short.	No change, this has previously been explored extensively during the development of the LRRC-QoL.
	Italian, 2	Questions are too general and vague, "psychological pain" is not investigated.	See Table 5.4.

	Dutch 2 Swedish 2	Pain, yes, without painkillers, no with painkillers. Add: with or without painkillers.	No change.
	New Zealand 6	The participant felt that these questions were no longer relevant now that they are 15 months post-surgery, however that these questions would have been relevant int the period following their operation.	No change.
	Swedish 7	No question about leg pain.	See Table 5.4.
	Canada HCP 1	Include issues related to pain and hernias.	See Table 5.4.
	Canada HCP 3	Pain in the vagina.	See Table 5.4.
	Singapore HCP 1	Pain on sitting is not represented.	See Table 5.4.
Urinary Symptoms Scale			
4. Have you had pain or a burning feeling when passing water/ urinating?	Dutch 2	Difficult to answer: no feeling/numbness, due to operation. Explore why– no feeling there, "neurosystem is down".	No change.
5. Have you had any unintentional release (leakage) of urine?	Spanish HCP 1	Suggested changing "*fuga*" to "*escape*" in question 5.	No change, not identified as an issue during forward-backward translation or patient interviews.
Overall scale	Italian 2	*« chiedere se il persone cerca/nota WC nei … dove passa »* Ask whether the person looks for/notices toilets when they are out and about.	See Table 5.4.
	Dutch 6	No question about frequency. Change to: "*How raak moet u planen ('s nachts)".*	See Table 5.4.
	Dutch 7	Urinary frequency during the night could be added. Change to: "*Moel u vaken in/of kleine beetje plannen*".	See Table 5.4.
	Dutch 8	Include urinary tract infections in the past year.	See Table 5.4.

	Swedish 3, 5, 7 and 8, New Zealand 8, Dutch 4 and 5, Spanish HCP 2	Questions are not applicable for patients with a urostomy, nephrostomy, or urinary catheter. Suggest adding "not applicable" or "go to next section".	No change for now, consider adding an option to move to next section if not applicable.
	New Zealand 4	The participant was experiencing urinary symptoms, namely nocturia, however they felt this was due to their age.	No change, the potential impact of age on urinary symptoms is recognised.
	Canada 1	Experiences sense of fullness in bladder.	No change, feel this is covered in the questions in relation to passing urine.
	Canada HCP 2	Suggested adding a question regarding urinary retention and incomplete emptying.	See Table 5.4.
	Singapore HCP 1	Faecaluria and pneumaturia not represented.	See Table 5.4.
Lower Limb Symptoms Scale			
6. Have you had any weakness of either or both legs?	Dutch 4	Add to question 6, "after surgery".	No change, questionnaire aims to also be applicable to patients who have not undergone surgery for LRRC.
7. Have you had any difficulty in walking?	Dutch 2	Difficult to answer when there is a loss of strength. Rephrase question 7: "*Had u in het algemeen moeite met lopen*" (Did you generally have trouble walking?).	No change, discussed with Dutch research team, this change would alter the meaning of the question.
8. Have you had any tingling or numbness in your feet or legs?	Canada 1	The patient felt this was more relevant when they were receiving chemotherapy and experiencing tingling in their feet due to peripheral neuropathy.	No change.

Overall scale	Danish 5	Patient stated that they are able to walk but not as long a distance as previously, they asked if the questionnaire wanted to know if they can walk at all or if they can walk in the way that they used to.	See Table 5.4.
	New Zealand 4	The patient also highlighted the impact of their lower limb symptoms on their function, noting that they are no longer able to get out of a low chair easily.	See Table 5.4.
	Canada HCP 1	Issues related to unsteadiness or falling.	See Table 5.4.
	Canada HCP 2	Issues related to limb oedema, such as heaviness or swelling.	See Table 5.4.
Other Symptoms			
9. Have you had any abnormal bleeding, discharge or faecal leakage from your rectum?	Spanish HCP 1	Suggested changing "*fuga*" to "*escape*" in question 9.	No change, not identified as an issue during forward-backward translation or patient interviews.
	Dutch 2 and 4	Add "anus/stoma" or a "not applicable" option.	No change, a skip option is included above item 9.
	Italian 2	*"Bisogna aggungeve "perdite di muco"* Need to add "*discharge of mucous*" as this is not covered currently.	Change implemented.
	New Zealand 5	This option was not relevant to the patient, they suggested changing the question prior to question 9 to *"Have you had surgery for recurrence?"*.	No change, patient may have had surgery for recurrence and still have a rectum or anus.
10. Have you had pain or discharge from your wound(s) or scar(s)?	Dutch 3	"Irrelevant" should be an option.	No change, response options are in keeping with EORTC modules.
	Swedish 3	Question 10 should include *"mucous discharge*".	No change following discussion with Swedish research team, term *"discharge"* felt to include mucous.
Overall scale	Swedish 5	The participant felt that the instructions were unclear, they missed the instruction, "*if not go to question 10*".	No change, the clinical team and other patients interviewed all found the guidance clear.

	Danish 2	The participant felt it was not obvious that they should only answer question 10 and that this question also included the anal wound.	No change, the clinical team and other patients interviewed all found the guidance clear.
Stoma Scale			
12. Have you felt embarrassed because of your stoma?	Swedish 3	Patient questioned the purpose of question 12.	No change, review during psychometric analysis.
	Dutch 5	Question 12 was hard to answer, as the term "opgelaten" was unclear. Rephrase to: "heb je moeite metje stoma?" Have you had trouble with your stoma?	Changed the term "opgelaten" to "geschaamd".
13. Have you had any problems caring for your stoma?	Dutch 2	Question 13 difficult to answer, technically "no problem" but emotionally, "a lot". Add a question: "*voelt u zich opgelaten of beperkt door uw stoma?"* (Do you ever feel let down or limited by your stoma?)	No change, this was not felt to reflect a specific concept.
Overall scale	Spanish HCP 1	Items related to stoma bag falling off or stoma bag leaks not represented.	See Table 5.4.
	Dutch 8	Add: "do you have pain near the ostomy?"	See Table 5.4.
	Dutch 9	No question about pain in the stoma region.	See Table 5.4.
	New Zealand 6	The patient stated that their ileostomy affected their sleep and felt that a question related to impact on sleep should be included.	See Table 5.4.
	Canada 1	Patient stated that their stoma has increased in size since their operation.	See Table 5.4.
	Canada HCP 2	Skin issues, such as excoriation, related to the stoma.	See Table 5.4.
Urostomy Scale			
16. Have you felt embarrassed because of your urostomy (urine bag), nephrostomy or urinary catheter?	Dutch 5	Question 16 was hard to answer, as the term "opgelaten" was unclear.	Changed the term "opgelaten" to "geschaamd".

17. Have you been dependent on others for caring for your urostomy (urine bag)?	Dutch 5	Questions 16 and 17 are confusing because the previous question is about multiple options, whereas question 17 is specific to one problem. Rephrase question 16 to: "hebt u moeite met uw urostoma?" Are you having trouble with your urostomy?	No change.
Overall scale	Spanish HCP 1	The scale heading does not represent all issues included, such as nephrostomies and catheters.	No change for now, consider adding this to the scale heading.
	Swedish 1 and 5	The participant had both a urostomy and nephrostomy and therefore found it difficult to answer the questions as their answers may be relevant to one but not the other.	No change, this was felt to be a relatively rare occurrence.
Sexual Interest Scale			
18. Have you been interested in sex?	Dutch 3	Question 18 should have an irrelevant option. Rephrase to current situation (sexually) with my partner.	No change, response options are in keeping with EORTC modules.
	Dutch 8	Please add option for question 18 "prefer not to answer this question".	No change, response options are in keeping with EORTC modules.
19. Have you had pain during sexual intercourse or other sexual activity?	Dutch 2	19 is confronting. Rephrase to *"Had u pijn tijdens de seks"* (Did you have pain during sex?)	Question 19 changed to "Heeft u pijn gehad tijdens de seks?"
	Swedish 1, 3, and 7 Dutch 1, 2, 5, 6, 7 and 8	The participant found that question 19 was not applicable, as there were no answers to indicate that they were not having sex. They would have liked to have had a question to indicate that it was not applicable/they were not having sex. They felt that if you do not have sex, you cannot answer the question, if you select the answer "never", this could be misinterpreted as having painless sex.	No change for now, consider adding a question to ask whether the patient is participating in sexual activity/able to have sex.
	Danish 4	Felt that this was not relevant in the first months after surgery.	No change, appreciate that these items may not be relevant to all patients at all times.
	New Zealand 3	The participant felt these questions were not relevant to them in relation to their age of 65 rather than in relation to their disease and treatment.	No change, other patients over the age of 65 may have an active sex life and therefore find this relevant.

	New Zealand 6	The participant felt that this question was not relevant as they do not have a partner and have no plans to have a partner.	No change for now, consider adding a question to ask whether the patient is participating in sexual activity/able to have sex.
	Canada 1	The patient felt that this was relevant given that they experience sexual interest but has difficulty having sexual intercourse due to erectile dysfunction following chemotherapy.	No change.
Overall scale	Swedish 2	The participant would like a question regarding whether you have received any help or guidance if you have experienced problems with sexual interest.	See Table 5.4.
	Spanish HCP 1	Patients in Spain often attend clinic with their family, including their children, and therefore it can be difficult to have an open discussion regarding sexual interest and function.	No change, this is not an issue specific to the LRRC-QoL.
	Singapore HCP 1	Discussing issues such as sexual interest and function is culturally taboo.	No change, agreed that these scales represent important issues and should remain.
	New Zealand 3	The participant felt that questions related to the impact on their relationship and support from partner not only in relation to sexual interest.	See Table 5.4.
Sexual Function Scale			
21. Have you had irritation or soreness in your vagina or vulva?	Dutch 2	Question 21, numbness due to surgery is not an option.	See Table 5.4.
23. Have you had ejaculation problems (e.g. dry ejaculation)?	New Zealand 5	The patient felt that questions related to erectile function were not linked only to sex as they experience erections during the night and also as a sign that they need to urinate. They suggested adding the following question, *"Have you had an erection caused by the need to urinate?".*	See Table 5.4.
Overall scale	Spanish HCP 1	Questions under female Sexual Function scale do not relate to sexual function.	No change, consider changing the name of the scale in future versions.

	Spanish HCP 1	Vaginal lubrication is not addressed.	See Table 5.4.
	Italian 2	"*These questions might be avoided*" Sexual function questions not relevant to participant, they also felt that sexual dysfunction should be better explained.	No change following further discussion with Italian research team.
	Italian 6	The patient was experiencing some sexual dysfunction related to age and felt a parameter should be introduced related to the person's age.	No change, other patients of same age may have an active sex life and therefore find this relevant.
	Italian 10, Swedish 7	"*valutare … s'e c'e'arrivira sessuale"* Evaluate whether there is sexually activity.	No change for now, consider adding an option to ask whether the patient is participating in sexual activity/able to have sex.
	Spanish 3	"*Es una de los cosas que mas me ha affectable*" It is one of the things that has affected me the most.	No change.
	Dutch 5	No sexual function anymore and so these questions are not relevant.	No change, appreciate that these items may not be relevant to all patients.
	Swedish 3	The participant felt the response options should be more nuanced.	No change, response options are in keeping with EORTC modules.
	Canada 1	The patient felt this was relevant and feels that chemotherapy affected their sexual function.	No change.
	Canada HCP 2	No question related to female orgasm.	See Table 5.4.
Psychological Impact Scale			
24. Have you felt physically less attractive as a result of your disease or treatment?	Canada 1	The patient felt this was very relevant, "it's not a pretty thing, let's be honest".	No change.

27. Have you felt uncertain about the future?	Dutch 2	In what perspective? Financial? Yes, but not emotionally now. Rephrase to "*voelde u zich hierdoor onzeker over de toekomst?"* (Did this make you feel insecure about the future ?)	See Table 5.4.
Overall scale	Spanish HCP 2	Consider adding an item related to the impact on family and relationships.	See Table 5.4.
	Dutch 3	Very important issue during follow-up. Not offensive, however it makes you think, what is the mental influence of the disease or treatment?	No change.
	Danish 3	The participant felt these questions activated thoughts about the future and of being able to take care of oneself.	See Table 5.4.
	New Zealand 5	The patient felt that the questions should be more specific about timelines in relation to surgery.	No change, timeframes were explored extensively during the development of the LRRC-QoL.
	Canada HCP 2	Issues related to low mood or depression.	See Table 5.4.
28. Have you worried about becoming dependent on others because of your illness?	Italian 6	"I would give five options so that the person could explain why he/she is worried"	No change, response options are in keeping with EORTC modules.
	Dutch 6	*"Very relevant, good question!"*	No change.
	Dutch 7	Add "*In de toekomst*" (In the future).	No change as this would alter the question.
	Swedish 2	The participant would like to add a question regarding what it would be like if you were sick/ill for the rest of your life.	No change, does not reflect a specific concept.
	Danish 6	The patient stated they were not concerned about themselves but were worried about their children's future.	See Table 5.4.
	New Zealand 5	The patient felt that this question was very generic and that the relationship that one was in would affect how one feels. *"If you are young and single you may be worried compared to someone in a stable relationship/ living circumstance, as your partner could provide care and support".*	No change, response options are in keeping with EORTC modules.

	Canada 1	The patient felt this was relevant as they felt their condition was debilitating; they are now unable to life things, including picking up their cat and therefore needed more support at home from their partner.	No change.
Healthcare Services Scale			
29. Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?	Dutch 3	Question 29 change "*was*" to "*bent*".	Changed to "was".
30. Were you satisfied with the knowledge and experience of your specialist team (Doctors/ Nurses/ Specialist Nurses/ Physiotherapists)?	Dutch 5	Question 30 difficult to answer, as participant found it hard to give an opinion on the level of expertise of the doctor, would prefer the question, "do you trust your phsyicians?" Rephrase question 30: *"had u vertrouwen in uw behandelend team?"*	No change, this has previously been tested during the development of the LRRC-QoL.
31. Were you satisfied with the speed of implementing medical tests and/or treatments?	Swedish 3	The participant suggested dividing question 31, as they felt one could be satisfied with the speed of the diagnostics but not the treatment and vice versa.	No change, issue not identified by other patients.
Overall scale	Spanish 2	"I spent many hours in the hospital, the treatment is important"	No change.
	Dutch 4	Difficult to answer as was the exact opposite in answer as the other questions.	No change.
	Dutch 6	Relevant but patients might not have been in hospital or in contact in the last 4 weeks. Please add "during diagnosis" instead of 4 weeks as might not be applicable.	No change, this has previously been explored extensively during the development of the LRRC-QoL.
	Swedish 2	The participant would like to add a question regarding whether health care providers have asked the patient about everything that was relevant to their disease.	See Table 5.4.

	New Zealand 7	The patient suggested adding a question related to patient experiences of community nursing and feeling supported in the community, “I feel well supported in the home”.	See Table 5.4.
	Canada 1	The patient felt this was relevant. They have experienced delays in their ileostomy reversal due to COVID-19 backlogs.	No change.

5.3.2.2.1 Content Validity

Fifty-two issues were identified during the pre-testing interviews. Five (9.6%) of these issues were felt to be represented within the current LRRC-QoL measure. A significant proportion (n=13, 25.0%) were identified during the original development of the LRRC-QoL provisional item pool and were subsequently removed from the questionnaire during the development and testing process. The LRRC-QoL was designed to be used in combination with the EORTC QLQ-C30 and several issues identified (n=14, 26.9%) are represented in this measure. Other issues were not identified during the LRRC-QoL development or represented in the EORTC QLQ-C30 and decisions regarding potential changes to the questionnaire are detailed in Table 5.4. Reasons for not adopting additional issues included them being identified by healthcare professionals only and not patients (n=8, 15.4%), issues being identified by only one patient (n=16, 30.8%), or the issues described not reflecting specific concepts (n=3, 5.8%).

Four potential changes were identified which could be introduced to future versions of the LRRC-QoL, these included:

1) Add a skip question to the Urinary Symptoms scale to prompt patients with a urostomy to move past these items,
2) Add a skip question or tick box prior to the Sexual Interest scale to confirm whether the patient has sex/is sexually active,
3) Change the name of the Urostomy scale to reflect its inclusion of nephrostomies, catheters, or other urinary devices,
4) Change the name of the female Sexual Function scale as the constituent items relate to vaginal symptoms.

Table 5.4: Issues identified during cognitive interviews

Issues Identified during Cross-Cultural Adaptation	Who the issue was identified by	Number of patients/ clinicians identifying this issue	Identified during LRRC-QoL Development?	Item represented in the EORTC QLQ-C30?	Provisional Item Pool for the LRRC-QoL or EORTC QLQ-C30 Item	Decision in Relation to LRRC-QoL
Issues related to hernias.	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.
Symptoms related to defaecation, such as incontinence and diarrhoea	Patient	1	Similar	Diarrhoea and constipation included.	**Current LRRC-QoL:** Have you had any abnormal bleeding or discharge from your rectum? **EORTC C30:** Have you had diarrhoea? Have you been constipated?	No change, similar issues included in the LRRC-QoL and represented in the EORTC C30.
Tiredness, lack of energy	Patients	2	Yes	Yes	**LRRC-QoL development:** Have you been tired? Have you lacked energy? **EORTC C30:** Were you tired? Did you need to rest?	No change, similar issues identified during LRRC-QoL development and represented in the EORTC C30.
Appetite	Patient	1	No	Yes	**EORTC C30:** Have you lacked appetite?	No change, represented in the EORTC C30.
Loss of taste	Patient	1	No	No		No change, not specific to LRRC and only identified by one patient.
Feeling sentimental or more vulnerable following surgery	Patient	1	Similar	No	**LRRC-QoL development:** Have you felt less confident?	No change, similar issues identified during LRRC-QoL development.

Problems related to the placement of their stoma and urostomy, such as being placed close together	Patient	1	No	No		No change, only relevant to patients who have had total pelvic exenteration and only identified by one patient.
Post-operative recovery	Patient	1	Yes	No	**LRRC-QoL development:** Are you satisfied with your length of recovery?	No change, identified during LRRC-QoL development.
Work and time off work	Healthcare professional	1	Yes	Yes	**LRRC-QoL development:** Have you been limited in doing either your work or daily activities?	No change, identified during LRRC-QoL development and represented in EORTC QLQ-C30.
	Patient	1			**EORTC C30:** Were you limited in doing either your work or other daily activities?	
Financial impact	Healthcare professional	1	Yes	Yes	**LRRC-QoL development and EORTC C30:** Has your physical condition or medical treatment caused you financial difficulties?	No change, identified during LRRC-QoL development and represented in the EORTC C30.
	Patients	2				
Metastatic disease	Patient	1	No	No		No change, does not reflect specific concept.
Urethral injury	Patient	1	No	No		No change, not likely to effect significant number of patients.
Being suitably informed about complications of surgery or counselling prior to surgery	Patients	2	Yes	No	**Current LRRC-QoL:** Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?	No change, represented in the current LRRC-QoL.
Rehabilitation	Patient	1	No	No		No change, does not reflect specific concept.

Space to share other diagnoses which may be relevant	Patient	1	No	No		No change, not specific to LRRC, can be provided by clinical data.
Poor memory	Patient	1	No	Yes	**EORTC C30:** Have you had difficulty remembering things?	No change, represented in the EORTC C30.
Current status, "*How are you doing right now?"*	Patient	1	No	Similar	**EORTC C30:** How would you rate your overall health during the past week? How would you rate your overall quality of life during the past week?	No change, similar items included in the EORTC C30.
Psychological pain or difficulty / Depression	Patient	1	Yes	Yes	**LRRC-QoL developmen**t: Have you felt depressed? Have you felt anxious? Have you felt angry?	No change, identified during LRRC-QoL development and represented in the EORTC C30.
	Healthcare professional	1			**EORTC C30:** Did you feel tense? Did you feel irritable? Did you feel depressed?	
Pain in relation to stoma	Patients	2	Similar	No	**Current LRRC-QoL:** Have you had abdominal pain?	No change, could be addressed in current item 1 (abdominal pain).
Leg pain	Patient	1	No	No		No change, issue only identified by one patient.
Pain in the vagina	Healthcare professional	1	Yes	No	**Current LRRC-QoL:** Have you had irritation or soreness in your vagina or vulva?	No change, issue not identified by patients, currently represented in LRRC-QoL item 21.
Pain on sitting	Healthcare professional	1	No	No		No change, issue identified by healthcare professional and not patients.
Include two separate questions regarding pain in the back and	Patient	1	Yes	No	**Current LRRC-QoL:** Have you had pain in your lower back and/or pelvis?	No change, issue only identified by one patient.

pain in the pelvis to be more specific.						
Looking for/noticing toilets when out and about	Patient	1	No	No		No change, likely to be related to continence or stoma issues which are included in current questionnaire. Issue also only identified by one patient.
Include a skip option for Urinary Symptoms scale for patients with a urostomy or catheter	Patients	8	No	No		No change currently, consider adding a skip question in future versions.
Urinary frequency	Patient	1	No	No		No change, issue only identified by one patient.
Urinary frequency during the night	Patient	1	No	No		No change, issue only identified by one patient.
Urinary tract infections in the past year	Patient	1	Similar	No	**Current LRRC-QoL:** Have you had pain or a burning feeling when passing water/urinating?	No change, similar issues identified during LRRC-QoL development and included in the current measure.
Fullness in the bladder/ urinary retention and incomplete emptying	Patient	1	No	No		No change, issue only identified by one patient and not clear if related to urinary retention/incomplete emptying.
	Healthcare professional	1				
Faecaluria and pneumaturia	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.
Unsteadiness or falling	Healthcare professional	1	Similar	Similar	**LRRC-QoL development:** Have you worried about loss of mobility because of your illness?	No change, similar issues identified during LRRC-QoL development and represented in the EORTC C30.

					EORTC C30: Do you have any trouble taking a long walk? Do you have any trouble taking a short walk outside of the house?	
Lower limb oedema; heaviness or swelling	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.
Physical activity	Patient	1	Yes	Yes	**LRRC-QoL development:** Have you had to modify your daily activities because of your illness? **EORTC C30:** Do you have any trouble taking a long walk?	No change, identified during LRRC-QoL development and represented in EORTC C30.
Reduction in walking distance	Patient	1	Similar	Yes	**LRRC-QoL development:** Have you worried about loss of mobility because of your illness? **EORTC C30:** Do you have any trouble taking a short walk outside of the house?	No change, similar issues identified during LRRC-QoL development and represented in EORTC C30.
Not able to get out of a low chair/lower limb function	Patient	1	Similar	Similar	**LRRC-QoL development:** Have you worried about loss of mobility because of your illness? **EORTC C30:** Do you need to stay in bed or a chair during the day?	No change, similar issues identified during LRRC-QoL development and represented in the EORTC C30.
Stoma bag leaks	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.

Feeling let down or limited by stoma, or psychological impact of a stoma	Patient	1	No	No		No change, issue only identified by one patient.
Impact of stoma on sleep	Patient	1	No	No		No change, issue only identified by one patient.
Increase in stoma size	Patient	1	No	No		No change, issue only identified by one patient.
Skin issues in relation to stoma	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.
Whether the patient has sex/is sexually active	Patients	9	No	No		No change currently, consider adding a skip question in future versions.
Receiving help or guidance related to sexual function	Patient	1	No	No		No change, issue only identified by one patient.
Fear of sex	Patient	1	Yes	No	**LRRC-QoL development:** Have you felt uncomfortable about being sexually intimate?	No change, identified during LRRC-QoL development.
Female orgasm	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.
Impact on relationships with family	Healthcare professional	1	Yes	Yes	**LRRC-QoL development and EORTC C30:** Has your physical condition or medical treatment interfered with your family life?	No change, identified during LRRC-QoL development and represented in the EORTC C30.
Support from partner	Patient	1	Similar	Similar	**LRRC-QoL development and EORTC C30:** Has your physical condition or medical treatment interfered with your family life?	No change, identified during LRRC-QoL development and represented in the EORTC C30.
Vaginal lubrication	Healthcare professional	1	No	No		No change, issue identified by healthcare professional only and not patients.

Vaginal numbness or pain	Patient	1	No	No		No change, issue only identified by one patient.
Erection caused by the need to urinate	Patient	1	No	No		No change, not likely to effect significant number of patients.
Concern for their children's future.	Patient	1	No	No		No change, issue only identified by one patient.
Healthcare professionals asking about everything relevant to their disease	Patient	1	Similar	No	**Current LRRC-QoL:** Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?	No change, similar issues identified during LRRC-QoL development and represented in the current measure.
Feeling well supported in the community/at home	Patient	1	No	No		No change, issue only identified by one patient.
Concern regarding health in the future.	Patients	2	Yes	No	**LRRC-QoL development:** Have you been worried about your health in the future? **Current LRRC-QoL:** Have you felt uncertain about the future?	No change, identified during LRRC-QoL development and similar issue represented in the current measure.

5.3.2.2.2 Face Validity and Acceptability: QQ-10 Responses

Table 5.5 demonstrates the overall mean Value and Burden Scores for the QQ-10, confirming the face validity and acceptability of the LRRC-QoL.

Table 5.5: QQ-10 Value and Burden scores

	Mean Value Score (0-100)	**SD**	**Mean Burden Score (0-100)**	**SD**
All participants	76.80	13.88	20.22	23.03

5.4 Discussion

This chapter details the successful cross-cultural adaptation of the LRRC-QoL into Danish, French, Italian, Dutch, Swedish, Urdu (India and Pakistan), Spanish, Mandarin (Singapore), Portuguese (Brazil), and for use in New Zealand and Canada. Meaning the LRRC-QoL can now be used in 10 languages across 14 countries, expanding its utility on an international platform and making it accessible to a wider cohort of patients experiencing LRRC and its treatment. The English-language version of the questionnaire has now undergone extensive cognitive testing in the UK, Australasia, and North America, and can therefore be considered acceptable for use in other English-speaking countries within these regions, such as Ireland and the USA. Patients completing the LRRC-QoL as an ePROM also reported no significant issues with the REDCap platform, indicating its acceptability as a mode of administration. In terms of the feedback from the interviews, specifically those related to the translation and wording of the questionnaires, there were very few changes required. Some minor modifications to the translation were implemented to the Dutch, Italian, and Mandarin versions, however, they were not

considered significant enough to require further testing with interviews. No comments are detailed from the Portuguese, Urdu, or French interviews as no issues were identified, in the case of the French interviews, this is likely due to patient representatives being involved in the translation process of the questionnaire.

In relation to the content validity of the LRRC-QoL, the results of these interviews confirm this crucial psychometric property in an international cohort of patients. Though a number of conceptual issues were identified, none were adopted into the questionnaire. There are robust reasons to support this decision, including the issues having previously been considered during the PROM development process, them being represented in the current measure or in the EORTC QLQ-C30, or them not being identified by sufficient numbers of patients to suggest their generalisability. The potential changes to the measure which were identified and considered for adoption related to the addition of skip questions or changes to the names of the scales. The results from the QQ-10 measure have also demonstrated the face validity and acceptability of the LRRC-QoL. Implementing the suggested changes would not alter the content validity of the LRRC-QoL and therefore would not require further pre-testing interviews. However, re-confirmation of the face validity may be required.

One of the key difficulties encountered in undertaking cross-cultural adaptation of the LRRC-QoL was reaching the EORTC advised target of 10-15 patients per version of the questionnaire (110). Given the rare nature of LRRC, a pragmatic decision was taken to accept a lower number of patients per version of the LRRC-QoL, provided there was evidence of stability in the responses to the cognitive interviews. Developing PROMs specifically for patients with rare diseases, such as LRRC is important given that these

patients experience a unique set of issues, as demonstrated by the development of the LRRC-QoL conceptual framework (106). Several guidelines exist with a view to ensuring that the processes for the development of PROMs result in measures which are high-quality and psychometrically robust (93, 107, 110, 112-114, 293). Though these guidelines represent a positive step and have advanced the quality of PROM development, the standards they set can be very difficult to satisfy in rare disease groups with a much smaller, often heterogenous populations eligible to participate in PROM development studies and studies evaluating the psychometric properties of PROMs. The Professional Society for Health Economics and Outcomes Research (ISPOR) have formed a taskforce for outcome measurement in rare disease clinical trials, resulting in a report outlining the challenges and potential solutions in determining clinical outcomes, such as PROs, in rare disease trials (290). Regarding cross-cultural adaptation, the original ISPOR guidelines advise recruiting 5-8 patients for each version of a questionnaire to pilot-testing/cognitive interviews (112), the task force for rare diseases highlights the difficulties of achieving these numbers of patients in a rare disease setting, advising that, "*If possible, conducting cognitive interviews with a small number of patients, caregivers, or clinicians within regions or cultures of interest will provide evidence of the relevance of the measure to different populations*". This approach was therefore adopted in the development of versions of the questionnaire where recruitment was particularly challenging, including Spain, Singapore, and Canada.

There are several strengths of this study, including the strong methodological approach to cross-cultural adaptation, particularly considering the challenges posed in this rare disease-setting. Translatability assessment proved invaluable to identify potential issues prior to undertaking further testing, this in combination with the thorough translation process employed is likely to account for the very small number of issues identified

during pre-testing from a cultural and linguistic perspective. The number of languages incorporated and the inclusion of lower-middle income countries such as India and Pakistan, offers the potential to assess disease-specific HrQoL in a wider and more diverse cohort of patients with LRRC. A further strength of the study is the heterogeneity of patients interviewed, having undergone a range of different surgical procedures and diversity in the neo-adjuvant treatments received. A limitation of the original LRRC-QoL development was that it was not undertaken in several languages, as advised by the EORTC (293). However, this has now been addressed and the changes applied during cross-cultural adaptation have been applied to ensure consistency across all versions of the LRRC-QoL.

Limitations of this study include cross-cultural adaptation not being completed for all the languages intended. Though the LRRC-QoL was translated into Russian, Telugu, Hindi, and Marathi, pre-testing did not occur for these versions. In the case of the Russian version, it was not possible to continue working with the team based in Saint Petersburg following the Russian invasion of Ukraine, as communication broke down and collaboration was sanctioned. The site working on the Hindi and Marathi versions of the questionnaire did not open to recruitment as it was not possible to agree a Data Sharing and Collaboration Agreement that would satisfy both institutions, this is further detailed in chapter 9. The site working on the Telugu version of the LRRC-QoL opened to recruitment but unfortunately failed to recruit patients into the pre-testing study, sites in America also failed to recruit to the study. The site in Ireland did not open due to a prolonged ethical approval process which was further complicated by Brexit. The small number of patients receiving palliative treatment included is a further limitation of the study, however this is a challenging group of patients to recruit given their burden of disease and poor prognosis.

The next stage in the ongoing development of the LRRC-QoL will consist of external validation to confirm the scale structure, reliability, validity, and responsiveness of the measure and is described in chapter 6 of this thesis. The success of this study supports the requirement to incorporate flexibility in the cross-cultural adaptation of PROMs in rare disease settings, as described in ISPOR guidance (290), and demonstrates the value of translatability assessment. This flexibility will also extend to including the 67 patients recruited to this study in the external validation analysis of the LRRC-QoL, these cohorts will be combined given the challenges of recruiting a large number of patients with LRRC. In the future, undertaking further cross-cultural adaptation of the LRRC-QoL in additional languages and cultures will further expand its utility and reach an even greater number of patients worldwide.

5.5 Conclusion

The LRRC-QoL has now undergone cross-cultural adaptation in 9 new languages and for use in 12 countries, in addition to the UK and Australia, in which the measure was originally developed. The measure has also demonstrated content validity, face validity, and acceptability in this international cohort. External validation of the LRRC-QoL will further confirm its additional psychometric properties and is described in chapter 6.

Chapter 6 External Validation of the LRRC-QoL in an International Cohort

6.1 Introduction

The psychometric analysis of the LRRC-QoL described in chapter 4 of this thesis resulted in a measure consisting of 29 items and nine scales. The measure demonstrated a robust scale-structure following both multi-trait and exploratory factor analyses, excellent reliability and temporal stability, measured by internal consistency using Cronbach's Alpha, and test-retest assessed through intraclass correlation. The LRRC-QoL demonstrated good convergent validity; confirming most of the hypotheses made in relation to correlation with the EORTC CR29 and FACT-C scales, as assessed using Pearson's Product Moment Correlation. The results for the known groups comparison demonstrated that the LRRC-QoL was able to discriminate between some clinically relevant groups but were affected by high rates of missing clinical data.

The aim of the current study was to confirm the generalisability, reliability, and validity of the LRRC-QoL in an external, international cohort. In addition to evaluating the responsiveness of the measure through conducting a prospective, longitudinal cohort study assessing HrQoL.

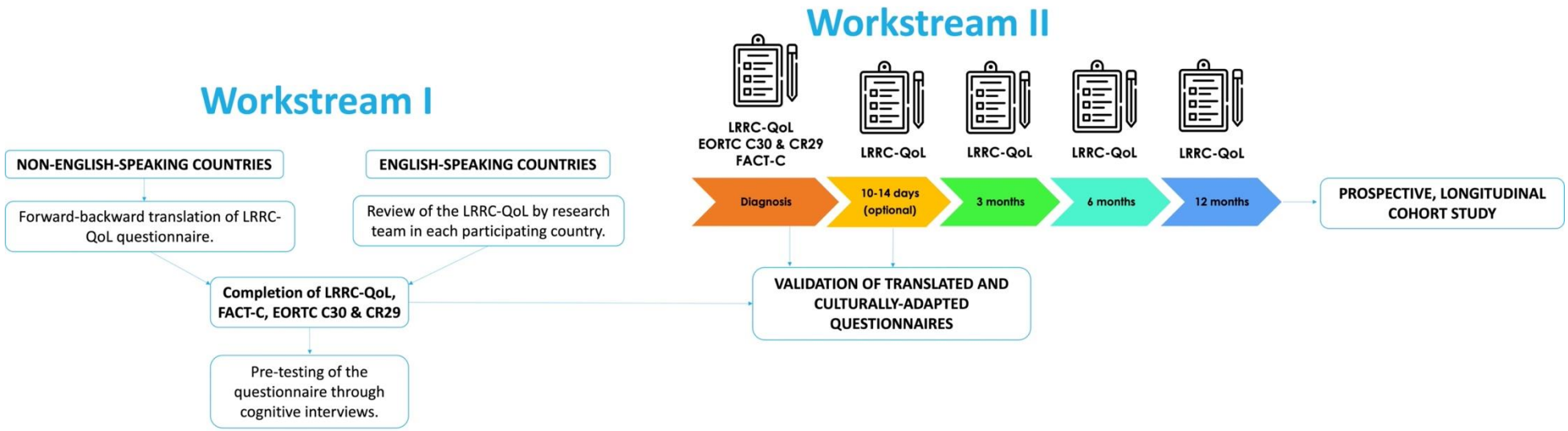
6.2 Methods

The data included in the external validation of the LRRC-QoL were collected via two workstreams summarised in Figure 6.1.

- **Workstream I**: cross-cultural adaptation of the LRRC-QoL
    - Patients recruited to the cross-cultural adaptation study described in chapter 5 were also included in the psychometric analysis of the LRRC-QoL questionnaire, utilising the responses to the PROMs collected prior to pre-testing interviews.
- **Workstream II**: a prospective, international, multi-centre cohort study of HrQoL in LRRC
    - HrQoL was assessed using the LRRC-QoL from baseline diagnosis through to 3-,6-, and 12-months.
    - The baseline data collected in this workstream were included in the external validation analysis, patients were also given the option to complete the LRRC-QoL at 10-14 days to enable test-retest reliability assessment of the measure.

Patients were recruited to the study from 25 centres in 13 countries including Brazil, Canada, Denmark, France, India, Italy, the Netherlands, New Zealand, Pakistan, Singapore, Spain, Sweden, and the UK.

Figure 6.1: Summary of workstreams I and II



6.2.1 Eligibility Criteria

The eligibility criteria for inclusion in workstream II were:

- age ≥ 18 years,
- with a new radiological and/or histological diagnosis of LRRC, or,
- have undergone treatment (surgery/chemotherapy/radiotherapy) for LRRC within the last 2 years,
- able to provide informed written consent to participate and,
- able to read and write in the target language.

Patients were excluded from the study if any of the following criteria were applicable:

- cognitive impairment,
- remission from treatment of PRC with no evidence of recurrence,
- receiving treatment for distant metastatic disease (i.e., liver, lung) following previous treatment of rectal cancer with no evidence of local recurrence.

6.2.2 Sample Size

Recommended guidelines advise that 5-10 patients should be recruited per item within a PROM to enable confirmatory factor analysis (CFA) (293). The LRRC-QoL consists of 29 items and therefore the target for recruitment was 320 patients with a 10% attrition rate.

6.2.3 Recruitment Strategies

Several recruitment strategies were employed during the delivery of the study and were frequently reviewed with a view to maximising recruitment, this process is described in

greater detail in chapters 9 and 10. Recruitment was intended to last for 12 months with a 12-month follow-up period.

6.2.4 Data Analysis

All data were analysed using SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA) and R Statistical Software (v4.2.3; R Core Team 2023) using the lavaan package (v0.6-7; Rosseel, 2012) (294) and mice package (v3.16.0; van Buuren and Groothuis-Oudshoorn, 2011) (295). Data analysis was undertaken sequentially, commencing with a descriptive analysis of the demographic and clinical data. The 29 items within the LRRC-QoL are scored on a Likert scale of 1-4 and overall scale scores comprise the sum of their constituent items. For most scales, a higher score indicates worse symptoms, excluding the Healthcare Services scale, for which a higher score indicates better experiences. The overall HrQoL score comprises the sum of all items excluding the Healthcare Services scale. Detailed scoring instructions can be found in Appendix 6.

6.2.4.1 Data Completeness

The first step in the analysis was assessment of data completeness at an item and scale level, the distribution of responses and for floor/ceiling effects. The criteria for acceptable levels of missing data were <10% for items, <50% for computable total scale scores and <80% for floor ceiling effects (296). Items and scales not meeting these criteria were excluded from the remaining steps of the psychometric analysis. Missing data below these levels were handled with multiple imputation (273, 295, 297, 298).

6.2.4.2 Scale Structure

The scale structure of the LRRC-QoL has been assessed in chapter 4 of this thesis through multi-trait scaling analysis and exploratory factor analysis (EFA).

6.2.4.2.1 Confirmatory Factor Analysis

Confirmatory factor analysis (CFA) was used to assess the reproducibility and predictability of the previously confirmed scale structure of the LRRC-QoL. CFA statistically assesses the fit of the hypothesised scale structure of the measure determined through multi-trait analysis and EFA. CFA was undertaken using the Diagonally Weighted Least Squares (DWLS) estimator given the ordinal nature of the data.

Goodness of Fit

Several goodness of fit indices were used to assess the goodness of fit of the overall model and of individual parameter estimates. These include Chi-squared (ch2) which evaluates the difference between the observed data and the proposed model. The root-mean-square-error-of approximation (RMSEA) which evaluates the fit of the model and compensates for model complexity, with lower values indicating good fit. Incremental indices such as the comparative fit index (CFI) and Tucker Lewis Index (TLI) compare the model to a baseline model with higher values desired. These values are summarised in Table 6.1.

Table 6.1: Measures of goodness of fit and desired values

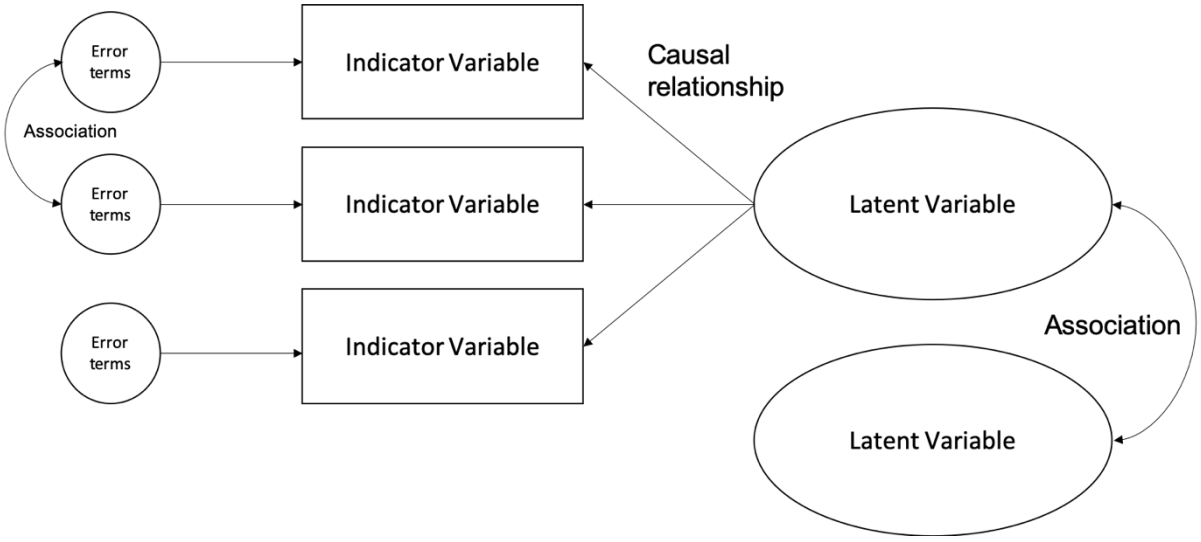
Measure	Values Indicating Goodness of Fit
Chi-squared	Lower value with the fewest degrees of freedom
Root-mean-square-error-of approximation (RMSEA)	<0.06
Comparative Fit Index (CFI)	0.90-0.95 adequate, >0.95 good
Tucker Lewis Index (TLI)	0.90-0.95 adequate, >0.95 good

Strain Analysis

Model strain analysis was used to establish whether items belong to their specified domain through examining relationships between questions; a positive relationship indicates that the questions all contribute to the domain. A negative relationship indicates that scores are going in opposite directions, demonstrating misfit, and identifying questions which do not belong within the domain. Strain analysis is able to identify whether external factors are influencing the relationships between the questions within a domain.

Results were represented diagrammatically to visually demonstrate the relationships between the variables. Latent variables, indicator variables and error terms (unique variance) are depicted by different shapes with different types of arrows being used to represent the relationships between variables, this is illustrated in Figure 6.2. Straight arrows arising from the latent variable to the indicator variable indicate that it is the latent variable that determines the indicator variable. Green lines indicate a positive relationship, whereas red lines indicate a negative relationship, the depth of shade denotes the strength of the relationship. Thicker lines/arrows also indicate stronger relationships. Curved double-headed arrows indicate covariance and dotted straight lines indicate a fixed parameter in the model. Variables or errors that are not connected diagrammatically are considered to be independent. Each pathway within the model was determined through multiple regression. All indicators must contribute to the total score of the latent variable similarly to be considered as measuring a single dimension.

Figure 6.2: Diagrammatic representation of strain analysis



6.2.4.3 Scale Reliability and Validity

Reliability, convergent validity, and known groups comparison analyses were undertaken in accordance with the methodology described in the psychometric analysis of the UK and Australian cohort data in chapter 4.

6.2.4.3.1 Scale Reliability

Reliability was assessed through the internal consistency of the scales, measured using Cronbach's Alpha, values of >0.7 are considered good. Reproducibility of the questionnaire was assessed using the test-retest measure at 10-14 days, measured using ICC, values of ≥0.7 are recommended.

6.2.4.3.2 Convergent Validity

Convergent validity was assessed as described in chapter 4, using Pearson's Correlation Coefficient (r) in a correlational analysis comparing the scales of the LRRC-QoL to those

of the EORTC QLQ-CR29 and FACT-C. Pearson's values of greater than 0.45 are considered highly correlated.

The a priori hypotheses described in chapter 4 were re-assessed, namely:

- The LRRC-QoL Psychological Impact scale would correlate well with the EORTC QLQ-CR29 Body Image scale and the FACT-C Emotional Well-Being scale.
- The LRRC-QoL Pain scale would correlate well with the FACT-C Physical Well-Being scale.
- The LRRC-QoL Urinary Symptoms scale would correlate well with the EORTC QLQ-CR29 Urinary frequency scale.
- The LRRC-QoL Stoma scale would correlate well with the EORTC QLQ-CR29 Frequency of Bowel Movements scale.

Two additional hypotheses were assessed:

- The LRRC-QoL Stoma scale would correlate well with the EORTC QLQ-CR29 Blood or Mucous in Stool scale.
- The LRRC-QoL Lower Limb Symptoms scale would correlate well with the FACT-C Physical Well-Being scale.

6.2.4.3.3 Known Groups Comparison

Demographic and clinical characteristics were used to identify groups of patients to assess whether the LRRC-QoL was able to distinguish between them using the independent t-

test to compare mean scores between two groups and ANOVA to compare mean scores in groups greater than two:

- Gender – male versus female,
- Pattern of recurrence – anterior, central, lateral, or posterior,
- Treatment intent – palliative versus curative,
- Presence of metastatic disease – metastatic disease versus no metastases,
- Pre-operative treatment for recurrence – no neoadjuvant treatment versus neoadjuvant treatment.

6.2.4.4 Responsiveness

Responsiveness is the ability of an instrument to illustrate changes over time, for instance changes in relation to patient condition such as disease progression or response to treatment. The standardised response mean (SRM) and effect size (ES) were used to assess the responsiveness of the LRRC-QoL at 3- and 6-months in patients undergoing surgical resection and patients receiving palliative treatment. The SRM is the ratio of the mean change to the standard deviation of that change and ES is the ratio of the mean change to the standard deviation of the initial measurement. The ES was used to interpret differences or changes in HrQoL following treatment. The higher the ES or SRM, the greater the level of sensitivity to change.

6.3 Results

Two hundred and four participants were recruited to the study from 13 countries. The patient demographics and clinical characteristics are detailed in Table 6.2 for each

workstream and overall. In relation to the overall cohort, there were 142 male patients (69.6%) and median age was 65 (IQR 13.0). Regarding employment, patients were most commonly retired (n=84, 41.2%) and the majority were married (n=111, 54.4%). Median interval between PRC and LRRC was 19 months (IQR 28.0) and median interval between diagnosis with LRRC and participation in the study was 4 months (IQR 8.0). All patterns of LRRC were represented in the overall cohort, including anterior (n=22, 10.8%), central (n=44, 21.6%), lateral (n=36, 17.6%), and posterior (n=37, 18.1%). Fifteen percent of patients had metastatic disease (n=31) and the majority of patients were treated for LRRC with curative intent (n=129, 63.2%). Twenty-eight patients (13.7%) were treated with palliative intent, of which seven patients were initially planned to undergo curative surgery however either developed disease progression or opted not to have surgery. In patients treated with curative intent, 64 (49.6%) had a R0 resection. Patients underwent a range of surgical procedures for LRRC which are further detailed in Appendix 5.

Table 6.2: Patient demographics and clinical characteristics

Variable	**Workstream I: Cross-cultural adaptation (n=67)**	**Workstream II: Prospective Cohort (n=137)**	**Combined Cohort (n=204)**
Demographics (%)			
Sex			
Male	43 (64.2)	99 (72.3)	142 (69.6)
Female	24 (35.8)	38 (27.7)	62 (30.4)
Median Age (IQR)	64.0 (12.0)	66.0 (12.0)	65.0 (13.0)
Country of Recruitment			
UK	0 (0.0)	104 (75.9)	104 (51.0)
Italy	10 (14.9)	6 (4.4)	16 (7.8)
Netherlands	10 (14.9)	16 (11.7)	26 (12.7)
France	8 (11.9)	2 (1.5)	10 (4.9)
New Zealand	7 (10.4)	2 (1.5)	9 (4.4)

Sweden	8 (11.9)	7 (5.1)	15 (7.4)
Canada	4 (6.0)	0 (0.0)	4 (2.0)
Spain	3 (4.5)	0 (0.0)	3 (1.5)
Denmark	7 (10.4)	0 (0.0)	7 (3.4)
Singapore	1 (1.5)	0 (0.0)	1 (0.5)
India	6 (9.0)	0 (0.0)	6 (2.9)
Pakistan	2 (3.0)	0 (0.0)	2 (1.0)
Brazil	1 (1.5)	0 (0.0)	1 (0.5)
Ethnicity			
White	42 (62.7)	122 (89.1)	164 (80.4)
Black	0 (0.0)	2 (1.5)	2 (1.0)
Asian	9 (13.4)	0 (0.0)	9 (4.4)
Other	1 (1.5)	1 (0.7)	2 (1.0)
Unknown	15 (22.4)	12 (8.8)	27 (13.2)
Marital status			
Married	35 (52.2)	76 (55.5)	111 (54.4)
Civil partnership	1 (1.5)	1 (0.7)	2 (1.0)
Living with partner	3 (4.5)	8 (5.8)	11 (5.4)
Widowed	2 (3.0)	11 (8.0)	13 (6.4)
Separated	0 (0.0)	5 (3.6)	5 (2.5)
Divorced	2 (3.0)	6 (4.4)	8 (3.9)
Single	4 (6.0)	17 (12.4)	21 (10.3)
Other	3 (4.5)	1 (0.7)	4 (2.0)
Unknown	17 (25.4)	12 (8.8)	29 (14.2)
Education status			
Secondary school	17 (25.4)	56 (40.9)	73 (35.8)
College	9 (13.4)	22 (16.1)	31 (15.2)
University	15 (22.4)	27 (19.7)	42 (20.6)
Other	9 (13.4)	15 (10.9)	24 (11.8)
Unknown	17 (25.4)	17 (12.4)	34 (16.7)

Employment status			
Self-employed	8 (11.9)	14 (10.2)	22 (10.8)
Looking after home/family	5 (7.5)	4 (2.9)	9 (4.4)
Full time employment	8 (11.9)	16 (11.7)	24 (11.8)
Part time employment	4 (6.0)	6 (4.4)	10 (4.9)
Unemployed	0 (0.0)	7 (5.1)	7 (3.4)
Sick leave	3 (4.5)	12 (8.8)	15 (7.4)
Retired	22 (32.8)	62 (45.3)	84 (41.2)
Other	0 (0.0)	4 (2.9)	4 (2.0)
Unknown	17 (25.4)	12 (8.8)	29 (14.2)
Treatment for Primary Rectal Cancer (%)			
Location of PRC (distance from anal verge)			
High rectal (>10cm)	21 (31.3)	31 (22.6)	52 (25.5)
Mid rectal (5.1-10cm)	18 (26.9)	27 (19.7)	45 (22.1)
Low rectal (0-5cm)	20 (29.9)	34 (24.8)	54 (26.5)
Unknown	8 (11.9)	45 (32.8)	53 (26.0)
Neo-adjuvant Treatment PRC			
None	25 (37.3)	48 (35.0)	73 (35.8)
Short course radiotherapy (SCRT)	9 (13.4)	3 (2.2)	12 (5.9)
Long course chemoradiotherapy (LCCRT)	21 (31.3)	26 (19.0)	47 (23.0)
Chemotherapy	3 (4.5)	6 (4.4)	9 (4.4)
SCRT followed by chemotherapy	0 (0.0)	2 (1.5)	2 (1.0)
LCCRT followed by chemotherapy	4 (6.0)	2 (1.5)	6 (2.9)
Chemotherapy followed by SCRT	0 (0.0)	1 (0.7)	1 (0.5)
Chemotherapy followed by LCCRT	0 (0.0)	4 (2.9)	4 (2.0)
Other	0 (0.0)	1 (0.7)	1 (0.5)
Unknown	5 (7.5)	44 (32.1)	49 (24.0)
Operation for PRC			
Local excision	2 (3.0)	6 (4.4)	8 (3.9)
Anterior resection	43 (64.2)	47 (34.3)	90 (44.1)
Abdominoperineal resection	11 (16.4)	21 (15.3)	32 (15.7)
Hartmann’s procedure	1 (1.5)	9 (6.6)	10 (4.9)
Pelvic exenteration	2 (3.0)	1 (0.7)	3 (1.5)
Other	3 (4.5)	11 (8.0)	14 (6.9)
Unknown	5 (7.5)	42 (30.7)	47 (23.0)

Margin status			
R0	53 (79.1)	70 (51.1)	123 (60.3)
R1	7 (10.4)	12 (8.8)	19 (9.3)
R2	0 (0.0)	3 (2.2)	3 (1.5)
Unknown	7 (10.4)	52 (38.0)	59 (28.9)
Adjuvant treatment for PRC			
None	29 (43.3)	53 (38.7)	82 (40.2)
Radiotherapy	1 (1.5)	1 (0.7)	2 (1.0)
Chemoradiotherapy	4 (6.0)	8 (5.8)	12 (5.9)
Chemotherapy	27 (40.3)	30 (21.9)	57 (27.9)
Unknown	6 (9.0)	45 (32.8)	51 (25.0)
Median interval between Primary and Recurrence in months (IQR)	17.0 (25.3)	20.0 (29.5)	19.0 (28.0)
Locally Recurrent Rectal Cancer (%)			
Median interval between diagnosis with LRRC and participation in the study (IQR)	6.0 (22.0)	4.0 (8.0)	4.0 (8.0)
Mode of detection			
Symptomatic	14 (20.9)	28 (20.4)	42 (20.6)
Surveillance	48 (71.6)	61 (44.5)	109 (53.4)
Other	0 (0.0)	3 (2.2)	3 (1.5)
Unknown	5 (7.5)	45 (32.8)	50 (24.5)
Pattern of LRRC			
Anterior	12 (17.9)	10 (7.3)	22 (10.8)
Central	16 (23.9)	28 (20.4)	44 (21.6)
Lateral	18 (26.9)	18 (13.1)	36 (17.6)
Posterior	11 (16.4)	26 (19.0)	37 (18.1)
Unknown	10 (14.9)	55 (40.1)	65 (31.9)
Presence of Metastatic disease			
Yes	14 (20.9)	17 (12.4)	31 (15.2)
No	48 (71.6)	74 (54.0)	122 (59.8)
Unknown	5 (7.5)	46 (33.6)	51 (25.0)
Number of Sites of Metastases			
1	11 (16.4)	15 (10.9)	26 (12.7)
2	3 (4.5)	2 (1.5)	5 (2.5)
Unknown	5 (7.5)	51 (37.2)	66 (32.4)
Not applicable	48 (71.6)	69 (50.4)	117 (57.4)

Sites of Metastases			
Liver	5 (35.7)	4 (23.5)	9 (29.0)
Lung	4 (28.6)	7 (41.2)	11 (35.5)
Bone	1 (7.1)	0 (0.0)	1 (3.2)
Liver and lung	3 (21.4)	0 (0.0)	3 (9.7)
Other	1 (7.1)	6 (35.3)	7 (22.6)
Treatment Intent			
Curative	57 (85.1)	72 (52.6)	129 (63.2)
Palliative	5 (7.5)	23 (16.8)	28 (13.7)
Unknown	5 (7.5)	42 (30.7)	47 (23.0)
Pre-operative Treatment			
None	10 (14.9)	24 (17.5)	34 (16.7)
Short course radiotherapy (SCRT)	5 (7.5)	3 (2.2)	8 (3.9)
Long course chemoradiotherapy (LCCRT)	22 (32.8)	26 (19.0)	48 (23.5)
Chemotherapy	10 (14.9)	9 (6.6)	19 (9.3)
SCRT followed by chemotherapy	1 (7.1)	1 (0.7)	2 (1.0)
LCCRT followed by chemotherapy	8 (11.9)	2 (1.5)	10 (4.9)
Chemotherapy followed by LCCRT	0 (0.0)	3 (2.2)	3 (1.5)
Immunotherapy	1 (1.5)	2 (1.5)	3 (1.5)
Other	1 (1.5)	3 (2.2)	4 (2.0)
Unknown	9 (13.4)	64 (46.7)	73 (35.8)
Margin Status			
R0	29 (50.9)	35 (48.6)	64 (49.6)
R1	7 (12.3)	5 (6.9)	12 (9.3)
R2	2 (3.5)	0 (0.0)	2 (1.6)
Unknown	19 (33.3)	32 (44.4)	51 (39.5)
Palliative Treatment			
Chemotherapy	2 (40.0)	9 (39.1)	11 (39.3)
Radiotherapy	0 (0.0)	6 (26.1)	6 (21.4)
Chemoradiotherapy	0 (0.0)	3 (13.0)	3 (10.7)
Best supportive care	2 (40.0)	0 (0.0)	2 (7.1)
Unknown	1 (20.0)	5 (21.7)	6 (21.4)

6.3.1 Data Completeness

Data completeness for the LRRC-QoL is demonstrated in Tables 6.3 and 6.4, at an item and scale level. The data completeness overall was high and only three items had rates of missing data >10%. Item 10, related to pain or discharge from wounds had a missing data rate of 25%, this may reflect the timing of recruitment to the study. Most patients were recruited around the time of diagnosis with LRRC, given that the median interval between PRC and LRRC was 19 months, a significant proportion of patients may not have been experiencing problems with wounds or scars at this time. As experienced during the psychometric analysis described in chapter 4, items related to personal issues, such as sexual function or interest, had higher rates of missing data. This included item 19, regarding pain during sexual intercourse, with a missing data rate of 27.9% and item 21, regarding irritation or soreness in the vagina or vulva, with a missing data rate of 11.3% in participants who identified as female. None of the items had response rates of >80% for single scores, meeting the criteria for floor/ceiling effects. All scales demonstrated data completeness of >50% (Table 6.4).

Table 6.3: Item level descriptive analysis

	N	Missing (%)	Mean	SD	Response Value Frequency (%)			
					1	2	3	4
Pain								
33. Abdominal pain	204	2 (1.0)	1.57	0.76	115 (56.4)	64 (31.4)	18 (8.8)	5 (2.5)
34. Lower back/pelvic pain	204	2 (1.0)	1.75	0.83	92 (45.1)	76 (37.3)	26 (12.7)	8 (3.9)
35. Perianal/buttock pain	204	2 (1.0)	1.81	0.98	102 (50.0)	54 (26.5)	29 (14.2)	17 (8.3)
Urinary Symptoms								
36. Urinary irritation	204	9 (4.4)	1.39	0.77	147 (72.1)	34 (16.7)	7 (3.4)	7 (3.4)
37. Urinary incontinence	204	11 (5.4)	1.59	0.86	119 (58.3)	47 (23.0)	21 (10.3)	6 (2.9)

Lower limb symptoms								
38. Lower limb weakness	204	2 (1.0)	1.66	0.92	118 (57.8)	47 (23.0)	24 (11.8)	13 (6.4)
39. Difficulty in walking	204	4 (2.0)	1.63	0.87	115 (56.4)	54 (26.5)	22 (10.8)	9 (4.4)
40. Lower limb numbness	204	4 (2.0)	1.79	0.95	101 (49.5)	56 (27.5)	29 (14.2)	14 (6.9)
Other Symptoms								
41. Leakage/discharge from rectum	147	12 (8.2)	1.59	0.77	76 (37.3)	40 (19.6)	17 (8.3)	2 (1.0)
42. Pain/discharge from wounds	204	51 (25.0)	1.28	0.64	123 (60.3)	20 (9.8)	7 (3.4)	3 (1.5)
Stoma								
12. Embarrassment from stoma	139	0 (0.0)	1.71	0.86	70 (50.4)	47 (33.8)	15 (10.8)	7 (5.0)
13. Problems caring for stoma	139	6 (4.3)	1.44	0.72	88 (63.3)	35 (25.2)	6 (4.3)	4 (2.9)
Urostomy								
15. Problems caring for urostomy	37	0 (0.0)	1.54	0.65	20 (54.1)	14 (37.8)	3 (8.1)	0 (0.0)
16. Embarrassment from urostomy`	37	0 (0.0)	1.46	0.61	22 (59.5)	13 (35.1)	2 (5.4)	0 (0.0)
17. Dependent on others for caring for urostomy	37	2 (5.4)	1.40	0.78	26 (70.3)	5 (13.5)	3 (8.1)	1 (2.7)
Sexual Interest								
18. Interest in sex	204	19 (9.3)	1.73	0.89	92 (45.1)	64 (31.4)	21 (10.3)	8 (3.9)
19. Pain during sexual intercourse	204	57 (27.9)	1.35	0.78	116 (56.9)	19 (9.3)	4 (2.0)	8 (3.9)
Sexual Function Scale								
20. Discharge or bleeding from vagina (women)	62	4 (6.5)	1.43	0.65	38 (61.3)	15 (24.2)	5 (8.1)	0 (0.0)
21. Irritation or soreness in vagina or vulva (women)	62	7 (11.3)	1.45	0.84	40 (64.5)	7 (11.3)	6 (9.7)	2 (3.2)
22. Erectile function (men)	142	9 (6.3)	2.86	1.17	26 (18.3)	22 (15.5)	29 (20.4)	56 (39.4)
23. Ejaculatory dysfunction (men)	142	12 (8.5)	2.42	1.35	54 (38.0)	15 (10.6)	13 (2.1)	48 (33.8)

Psychological Impact								
24. Attractiveness	204	4 (2.0)	2.18	1.03	61 (29.9)	75 (36.8)	36 (17.6)	28 (13.7)
25. Worry about results	204	2 (1.0)	2.47	0.98	32 (15.7)	83 (40.7)	49 (24.0)	38 (18.6)
26. Worry about future treatments	204	3 (1.5)	2.58	1.04	35 (17.2)	62 (30.4)	56 (27.5)	48 (23.5)
27. Uncertainty about the future	204	2 (1.0)	2.72	1.05	31 (15.2)	54 (26.5)	59 (28.9)	58 (28.4)
Individual Item								
28. Worry about becoming dependent on others	204	3 (1.5)	2.48	1.06	42 (20.6)	66 (32.4)	48 (23.5)	45 (22.1)
Healthcare Services								
29. Satisfaction with information	204	1 (0.5)	3.44	0.76	6 (2.9)	16 (7.8)	65 (31.9)	116 (56.9)
30. Satisfaction with knowledge	204	1 (0.5)	3.58	0.68	4 (2.0)	10 (4.9)	53 (26.0)	136 (66.7)
31. Satisfaction with speed of implementation	204	1 (0.5)	3.28	0.90	12 (5.9)	25 (12.3)	61 (29.9)	105 (51.5)

Table 6.4: Data completeness for scales

Scale	**Total No of Items in Scale**	**Data Completeness (%)**	**Possible Score Range**	**Observed Score Range**	**Mean Score**	**SD**
Pain	3	98.5	3 – 12	3 – 11	5.11	1.95
Urinary Symptoms	2	94.6	2 – 8	2 – 8	2.97	1.30
Lower Limb Symptoms	3	97.5	3 – 12	3 – 12	5.06	2.15
Stoma	2	94.0	0 – 8	0 – 7	3.06	1.27
Urostomy	3	94.6	0 – 12	0 – 7	4.32	1.40
Sexual Function						
Female	2	87.1	2 – 8	2 – 6	2.79	1.32
Male	2	90.8	2 – 8	2 – 8	5.19	2.21

Psychological Impact	4	97.5	4 – 16	4 – 16	9.95	3.33
Healthcare Services	3	99.5	3 – 12	3 – 12	10.30	2.03

6.3.2 Scale Structure

The scale structure of the LRRC-QoL was evaluated through CFA using the DWLS estimator in R lavaan package. It was not possible to complete CFA in the external validation cohort as the sample size was not sufficient. This dataset was therefore combined with data from the cohort of 117 patients in the original validation of the LRRC-QoL, described in chapter 4. Even with this combined dataset of 321 patients, it was not possible to include the gender-specific Sexual Function scales within the model due to the small subsets of patients responding to the items within these scales. CFA was therefore undertaken using a model based on eight of the nine LRRC-QoL scales.

6.3.2.1 Goodness of Fit

The values for the indices listed in Table 6.5 suggest excellent goodness of fit in the adapted model (excluding the gender-specific Sexual Function scales) when assessed in a combined dataset of 321 patients. This included a relatively low chi-squared value with 181 degrees of freedom, a very low RMSEA of 0.000, a high CFI of 1.000 and TLI of 1.511.

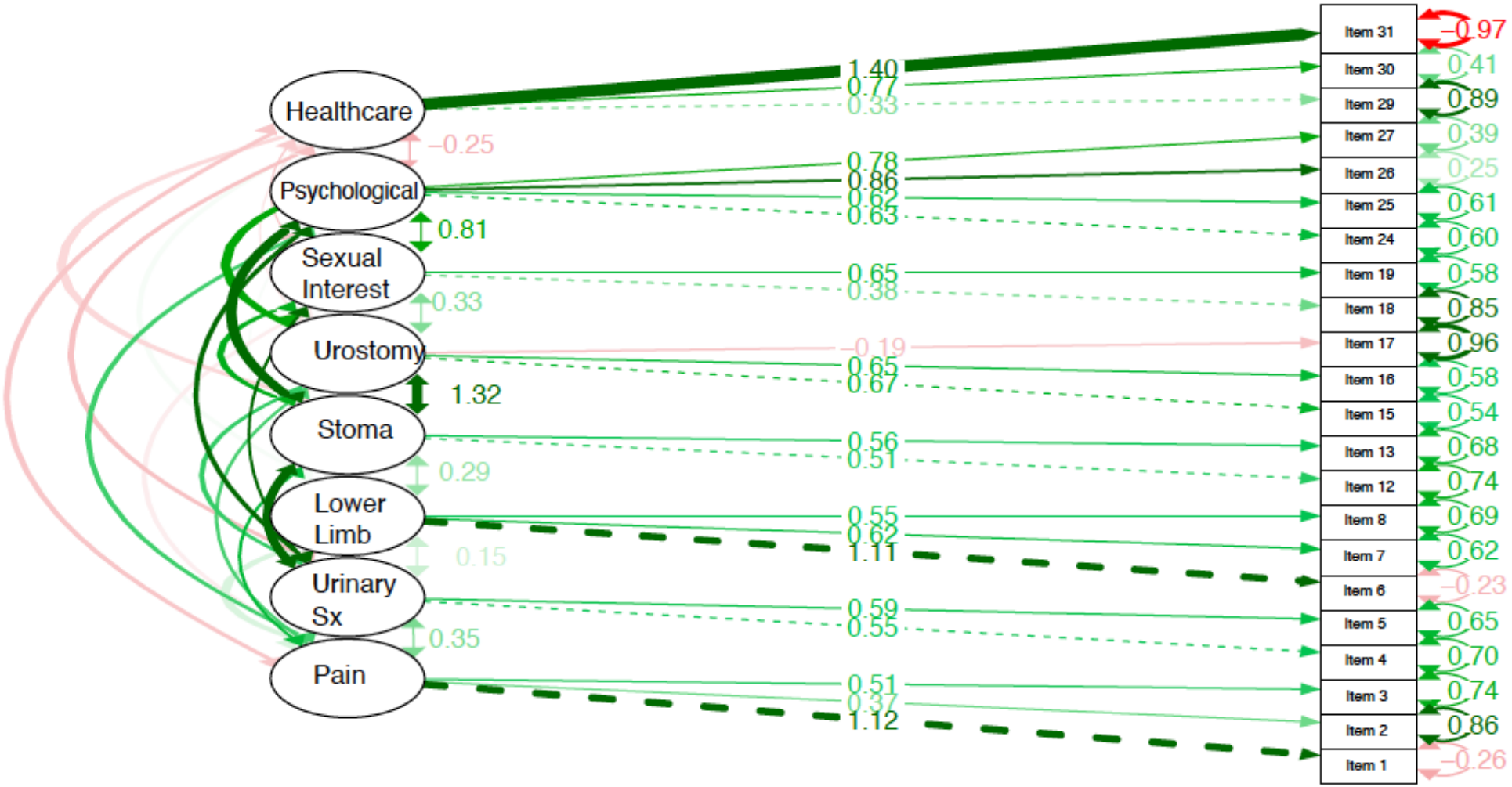
Table 6.5: Goodness of fit for the combined datasets

Measure	Value
Chi-squared	Test statistic of 113.131 (p = 1.000), with 181 degrees of freedom
Root-mean-square-error-of approximation (RMSEA)	0.000
Comparative Fit Index (CFI)	1.000
Tucker Lewis Index (TLI)	1.511

6.3.2.2 Strain Analysis

The results of the strain analysis are portrayed in Figure 6.3. Overall, they support the existing scale structure of the LRRC-QoL. The results demonstrate negative correlations between the Healthcare Services scale and other scales. This was anticipated given that higher scores in this scale indicate better experiences, whereas higher scores in the other scales indicate worse symptoms. The sexual interest and pain scales also demonstrated a negative correlation. The double-headed arrows between items demonstrate the correlations between them, overall, the majority of items within each scale were positively correlated with each other. The straight arrows from the scales to the items denote strain coefficient and confirm that the items within each scale load onto the single underlying factor identified in the previous EFA and multi-trait analyses.

Figure 6.3: Strain analysis



6.3.3 Scale Reliability

The majority of the LRRC-QoL scales demonstrated good reliability, with Cronbach's Alpha values either close to or greater than 0.7 (see Table 6.6). However, the Urinary Symptoms, Stoma, Urostomy, and Sexual Interest scales did not meet the criteria for reliability, with values of 0.28 – 0.43. In relation to test-retest reliability, median interval between LRRC-QoL completion was 11 (IQR 7.0) days. Most ICC values were >0.7, indicating good temporal stability. The Healthcare Services scale had an ICC of 0.54, it is possible that participants had contact with healthcare services during the 10-14 days between LRRC-QoL completions, which may have affected their responses. The Urostomy and Female Sexual Function scales also demonstrated ICC values of <0.6, these results could be limited by low numbers of patients responding to these scales.

Table 6.6: Scale reliability

Scale	Cronbach's Alpha (95% Confidence Intervals)	ICC (95% Confidence Intervals)
Pain	0.616 (0.515 – 0.700)	0.883 (0.815 – 0.927)
Urinary Symptoms	0.433 (0.252 – 0.571)	0.798 (0.691 – 0.871)
Lower Limb Symptoms	0.680 (0.596 – 0.750)	0.809 (0.706 – 0.878)
Stoma	0.419 (0.181 – 0.588)	0.721 (0.551 – 0.833)
Urostomy	0.280 (-0.261 – 0.613)	0.535 (-0.059 – 0.849)
Sexual Interest	0.357 (0.110 – 0.536)	0.642 (0.622 – 0.874)
Female Sexual Function	0.713 (0.506 – 0.834)	0.496 (-0.079 – 0.823)
Male Sexual Function	0.673 (0.537 – 0.769)	0.784 (0.647 – 0.872)
Psychological Impact	0.829 (0.787 – 0.865)	0.847 (0.762 – 0.903)
Healthcare Services	0.828 (0.783 – 0.865)	0.541 (0.347 – 0.690)

6.3.4 Scale Validity

6.3.4.1 Convergent Validity

The majority of the a priori hypotheses were confirmed in the convergent validity analyses, as demonstrated in Tables 6.7-6.8. These results were similar to those described in chapter 4; two hypotheses were not confirmed, these were the anticipated correlations between the LRRC-QoL Urinary Symptoms scale and EORTC QLQ-CR29 Urinary Frequency scale (r=0.301, p=0.000), and between the LRRC-QoL Stoma scale and EORTC QLQ-CR29 Frequency of Bowel Movements scale (r=0.375, p=0.000). In some instances, a Pearson's value of less than -0.45 was considered significant given the inverse scoring method utilised for the LRRC-QoL scale scores compared with the other measures.

Additional strong correlations which were not previously hypothesised were identified, these included correlations between:

- The LRRC-QoL Psychological Impact scale and the FACT-C Physical Well-Being (r=-0.566, p=0.000) and Functional Well-Being scales (r=-0.528, p=0.000).

Table 6.7: Convergent validity between the LRRC-QoL and EORTC QLQ-CR29 scales

EORTC QLQ-CR29 Scales		LRRC-QoL Scales									
		Pain	Urinary Symptoms	Lower Limb Symptoms	Stoma	Urostomy	Sexual Interest	Female Sexual Function	Male Sexual Function	Psychological Impact	Healthcare Services
Urinary Frequency	r	0.178	0.301*	0.125	0.074	0.097	-0.020	0.256	0.107	0.083	0.019
	P value	0.015	0.000	0.089	0.413	0.605	0.804	0.066	0.235	0.263	0.799
	95% CI	0.035 – 0.317	0.163 – 0.441	-0.019 – 0.271	-0.107 – 0.259	-0.250 – 0.421	-0.180 – 0.140	-0.020 – 0.581	-0.071 – 0.286	-0.062 – 0.227	-0.125 – 0.162
Blood / mucus in stool	r	0.168	0.162	0.252	0.463*	0.372	0.387	0.565	-0.072	0.297	-0.098
	P value	0.020	0.026	0.000	0.000	0.030	0.000	0.000	0.425	0.000	0.181
	95% CI	0.026 – 0.307	0.020 – 0.304	0.112 – 0.393	0.292 – 0.587	0.041 – 0.754	0.235 – 0.514	0.248 – 0.593	-0.301 – 0.128	0.160 – 0.437	-0.237 – 0.045
Body Image	r	0.331	0.232	0.368	0.423	0.038	0.043	0.253	0.194	0.627*	-0.264
	P value	0.000	0.001	0.000	0.000	0.829	0.584	0.067	0.029	0.000	0.000
	95% CI	0.195 – 0.467	0.094 – 0.381	0.238 – 0.510	0.264 – 0.580	-0.327 – 0.406	-0.118 – 0.209	-0.018 – 0.503	0.022 – 0.402	0.516 – 0.741	-0.395 - - 0.123
Frequency of Bowel Movements	r	0.182	0.116	0.220	0.375*	0.301	0.073	0.332	0.073	0.228	-0.071
	P value	0.014	0.122	0.003	0.000	0.089	0.363	0.019	0.427	0.002	0.341
	95% CI	0.036 – 0.318	-0.031 – 0.259	0.079 – 0.374	0.230 – 0.587	-0.061 – 0.813	-0.085 – 0.232	0.062 – 0.647	-0.103 – 0.242	0.084 – 0.370	-0.214 – 0.075

Green shading indicates the correlations identified, an Asterix* marks the a priori hypothesised correlations

Table 6.8: Convergent validity between the LRRC-QoL and FACT-C scales

FACT-C Scales		LRRC-QoL Scales									
		Pain	Urinary Symptoms	Lower Limb Symptoms	Stoma	Urostomy	Sexual Interest	Female Sexual Function	Male Sexual Function	Psychological Impact	Healthcare Services
Physical Well Being	r	-0.586*	-0.411	-0.491*	-0.394	-0.329	0.144	-0.259	-0.101	-0.566	0.207
	P value	0.000	0.000	0.000	0.000	0.061	0.075	0.073	0.260	0.000	0.005
	95% CI	-0.693 - -0.458	-0.553 - -0.280	-0.608 - -0.356	-0.535 - -0.218	-0.560 – 0.014	-0.013 – 0.265	-0.442 – 0.020	-0.290 – 0.079	-0.665 - -0.430	0.066 – 0.361
Social Well Being	r	-0.215	-0.039	-0.313	-0.243	0.055	0.040	-0.280	0.005	-0.316	0.304
	P value	0.004	0.601	0.000	0.007	0.762	0.622	0.051	0.954	0.000	0.000
	95% CI	-0.359 - -0.072	-0.192 – 0.112	-0.453 - -0.173	-0.399 - -0.066	-0.373 – 0.505	-0.109 – 0.182	-0.451 – 0.001	-0.182 – 0.193	-0.450 - -0.174	0.169 – 0.457
Emotional Well Being	r	-0.301	-0.226	-0.329	-0.440	-0.119	0.058	-0.325	0.058	-0.702*	0.240
	P value	0.000	0.002	0.000	0.000	0.509	0.477	0.023	0.522	0.000	0.001
	95% CI	-0.434 - -0.157	-0.375 - -0.083	-0.454 - -0.184	-0.562 - -0.260	-0.467 – 0.237	-0.090 – 0.191	-0.512 - -0.040	-0.124 – 0.243	-0.784 - -0.580	0.100 – 0.395
Functional Well Being	r	-0.399	-0.148	-0.425	-0.448	-0.044	0.268	-0.046	-0.135	-0.528	0.287
	P value	0.000	0.047	0.000	0.000	0.808	0.001	0.752	0.132	0.000	0.000
	95% CI	-0.533 - -0.263	-0.302 - -0.002	-0.558 - -0.292	-0.602 - -0.284	-0.399 – 0.313	0.102 – 0.378	-0.317 – 0.231	-0.305 – 0.041	-0.643 - -0.397	0.151 – 0.441
	r	-0.302	-0.207	-0.253	-0.411	-0.693	0.157	-0.184	-0.258	-0.357	0.239

Colorectal Scale	P value	0.000	0.005	0.001	0.000	0.000	0.052	0.206	0.004	0.000	0.001
	95% CI	-0.436 - -0.159	-0.357 - -0.063	-0.384 - -0.107	-0.589 - -0.253	-0.828 - -0.371	-0.001 – 0.280	-0.490 – 0.109	-0.412 - -0.081	-0.481 - -0.213	0.096 – 0.382

Green shading indicates the correlations identified, an Asterix* marks the a priori hypothesised correlations

6.3.4.2 Known Groups Comparison

The LRRC-QoL was able to identify significant differences in the clinical and demographic groups identified (Tables 6.9-6.11). The Psychological Impact scale demonstrated significantly higher scores, indicating worse psychological impact, in female patients. Whereas male patients reported worse sexual function. Patients with a lateral pattern of LRRC had significantly higher scores for the Lower Limb scale, indicating greater symptom burden. Patients who had received pre-operative oncological treatment for LRRC had significantly higher scores in the Stoma scale, denoting higher levels of embarrassment and difficulties caring for their stoma. The Healthcare Services scale demonstrated worse scores in patients without metastatic disease, indicating worse healthcare experiences.

Table 6.9: Known groups comparison for the Pain, Urinary Symptoms, and Lower Limb Symptoms scales

	Pain				**Urinary Symptoms**				**Lower Limb Symptoms**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	141	4.94	1.93	0.060	140	2.89	1.26	0.167	141	4.99	2.18	0.435
Female	62	5.50	1.95		62	3.16	1.38		62	5.24	2.07	
Pattern of Recurrence												
Anterior	22	5.45	1.82	0.159	22	2.82	0.96	0.691	22	4.09	1.66	0.030
Central	44	4.77	1.89		43	3.19	1.53		44	4.50	1.58	
Lateral	36	4.86	1.78		36	3.08	1.32		36	5.53	2.25	
Posterior	37	5.59	1.98		37	2.92	1.28		37	4.95	2.16	
Presence of Metastatic Disease												
Yes	28	4.96	1.69	0.636	28	3.11	1.34	0.839	28	4.54	1.82	0.312
No	122	5.15	1.87		121	3.05	1.35		122	4.97	2.07	
Treatment Intent												
Palliative	28	4.86	1.56	0.426	27	3.15	1.23	0.744	28	5.36	2.03	0.193
Curative	129	5.17	1.95		129	3.05	1.38		129	4.81	2.02	
Pre-operative Treatment												
None	34	4.71	1.77	0.136	34	3.12	1.57	0.814	34	4.53	1.66	0.245
Yes	97	5.28	1.96		97	3.05	1.35		97	5.00	2.13	

Green shading indicates statistically significant results.

Table 6.10: Known groups comparison for the Stoma, Urostomy, and Sexual Interest scales

	Stoma				**Urostomy**				**Sexual Interest**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	92	2.91	1.21	0.051	29	4.14	1.30	0.123	123	3.00	1.30	0.162
Female	48	3.35	1.34		8	5.00	1.60		52	2.67	1.64	
Pattern of Recurrence												
Anterior	17	2.59	1.23	0.181	5	3.80	0.84	0.230	22	2.91	1.48	0.839
Central	22	3.23	1.31		7	5.00	1.53		36	2.75	1.38	
Lateral	24	2.75	1.07		8	3.75	1.39		32	2.97	1.49	
Posterior	27	3.30	1.38		5	3.60	1.34		32	2.69	1.20	
Presence of Metastatic Disease												
Yes	18	3.17	1.42	0.661	4	4.50	1.91	0.568	24	2.46	1.44	0.083
No	81	3.01	1.33		22	4.05	1.36		105	3.05	1.50	
Treatment Intent												
Palliative	22	3.36	1.43	0.291	6	3.83	0.98	0.470	24	2.67	1.31	0.348
Curative	83	3.02	1.31		22	4.32	1.52		112	2.98	1.52	
Pre-operative Treatment												
None	24	2.50	0.98	0.012	5	4.40	1.67	0.932	29	2.97	1.30	0.973
Yes	61	3.28	1.36		18	4.33	1.50		86	2.98	1.60	

Table 6.11: Known groups comparison for the Sexual Function, Psychological Impact, and Healthcare Services scales

	Sexual Function				**Psychological Impact**				**Healthcare Services**			
	N	Mean	SD	P value	N	Mean	SD	P value	N	Mean	SD	P value
Gender												
Male	134	5.19	2.21	0.00	141	9.50	3.16	0.003	142	10.31	2.05	0.908
Female	58	2.79	1.32		62	10.97	3.50		62	10.27	2.00	
Pattern of Recurrence												
Anterior	21	4.33	2.37	0.591	22	9.09	3.12	0.539	22	9.95	2.44	0.163
Central	43	3.95	2.14		44	9.32	3.50		44	10.93	1.42	
Lateral	33	4.48	2.51		36	9.86	2.90		36	10.42	1.73	
Posterior	36	2.67	2.56		37	10.16	3.35		37	10.11	2.35	
Presence of Metastatic Disease												
Yes	26	3.81	2.14	0.090	28	9.14	3.11	0.263	28	11.14	1.46	0.039
No	115	4.67	2.36		122	9.93	3.38		122	10.32	1.97	
Treatment Intent												
Palliative	25	4.52	2.49	0.807	28	9.18	3.64	0.237	28	10.43	2.13	0.927
Curative	122	4.39	2.32		129	10.00	3.25		129	10.47	1.85	
Pre-operative Treatment												
None	31	4.06	2.28	0.368	34	9.44	3.26	0.170	34	10.91	1.64	0.094
Yes	92	4.50	2.34		97	10.33	3.22		97	10.29	1.92	

6.3.5 Responsiveness

Table 6.12 details the changes in the LRRC-QoL total score and its scale scores at 3- and 6-months for the overall cohort of patients, in addition to subgroups of patients undergoing surgical resection and patients receiving palliative treatment. Notably, an increase in score signifies worsening in symptoms for all LRRC-QoL scales, except the Healthcare Services scale, where an increase in score signifies better experiences, and Sexual Interest scale, where an increase signifies increased sexual interest. The HrQoL score comprises the total score for the LRRC-QoL excluding the Healthcare Services scale which measures healthcare experiences. It was not possible to assess Urostomy or Female Sexual Function scale scores for all subgroups of patients due to small sample sizes.

Patients who underwent surgery demonstrated significant deterioration in their overall HrQoL, as detailed by the HrQoL total score. This was more pronounced at 3-months (p=0.00, ES 0.57, SRM 0.50) compared with 6-months (p=0.01, ES 0.42, SRM 0.46). Conversely, patients receiving treatment with palliative intent reported an increase in their overall HrQoL at 6-months (p=0.01, ES 0.37, SRM 1.11) compared to baseline. Patients who had undergone surgery for LRRC also reported worse pain at 3-months (p=0.06, ES 0.47, SRM 0.29) and a significantly increased burden of lower limb symptoms at both 3 (p=0.00, ES 1.00, SRM 0.58) and 6-months (p=0.00, ES 1.30, SRM 0.66). Patients receiving treatment with palliative intent reported a significant improvement in lower limb symptoms at 6-months (p=0.03, ES 0.42, SRM 0.82). This patient group also reported a significant improvement in stoma-related issues at 6-months (p=0.02, ES 0.96, SRM 1.23).

Regarding the Sexual Interest scale, patients who had undergone surgery reported reduced scores at 3-months (p=0.04, ES 0.32, SRM 0.37), denoting reduced sexual interest. This patient group also reported an improvement in psychological symptoms at 3- and 6-months (p=0.06, ES 0.31, SRM 0.34). Finally, in relation to the Healthcare Services scale, scores were significantly reduced, indicating worse experiences, at 3 (p=0.00, ES 0.52, SRM 0.55) and 6-months (p=0.01, ES 0.81, SRM 0.51) in patients undergoing surgery.

Table 6.12: Responsiveness

	3-months					6 -months				
	n	**Mean change**	**P value**	**ES**	**SRM**	**n**	**Mean change**	**P value**	**ES**	**SRM**
LRRC-QoL Total										
Overall	85	1.24	0.15	0.16	0.16	59	0.81	0.42	0.10	0.11
Surgical	43	3.70	0.01	0.49	0.43	33	2.52	0.09	0.31	0.31
Palliative	14	-1.50	0.36	0.16	0.26	10	-5.20	0.00	0.49	1.25
HrQoL Total										
Overall	85	1.94	0.03	0.23	0.24	59	1.81	0.08	0.20	0.23
Surgical	43	4.49	0.00	0.57	0.50	33	3.79	0.01	0.42	0.46
Palliative	14	-0.93	0.57	0.09	0.15	10	-4.3	0.01	0.37	1.11
Pain Scale										
Overall	85	0.53	0.06	0.30	0.21	59	0.53	0.07	0.26	0.24
Surgical	43	0.79	0.06	0.47	0.29	33	0.58	0.19	0.27	0.23
Palliative	14	0.00	1.00	0.00	0.00	10	0.50	0.46	0.29	0.24
Urinary Symptoms Scale										
Overall	84	0.14	0.35	0.12	0.10	59	-0.12	0.62	0.09	0.07
Surgical	43	0.14	0.60	0.09	0.08	33	0.12	0.76	0.07	0.05
Palliative	14	0.43	0.11	0.68	0.46	10	0.10	0.73	0.15	0.11
Lower Limb Symptoms Scale										

Overall	85	0.79	0.00	0.40	0.32	59	1.08	0.01	0.50	0.36
Surgical	43	1.63	0.00	1.00	0.58	33	2.22	0.00	1.30	0.66
Palliative	14	-0.14	0.73	0.07	0.09	10	-0.90	0.03	0.42	0.82
Stoma Scale										
Overall	53	0.00	1.00	0.00	0.00	35	-0.46	0.11	0.33	0.28
Surgical	23	0.17	0.57	0.14	0.12	18	-0.28	0.52	0.20	0.16
Palliative	11	-0.45	0.36	0.29	0.29	7	-1.57	0.02	0.96	1.23
Urostomy Scale*										
Overall	9	0.22	0.76	0.17	0.11	4	0.00	1.00	0.00	0.00
Sexual Interest Scale										
Overall	69	-0.38	0.02	0.36	0.30	46	-0.26	0.16	0.25	0.21
Surgical	35	-0.37	0.04	0.32	0.37	25	-0.12	0.61	0.12	0.10
Palliative	12	-0.75	0.15	0.57	0.45	8	-0.88	0.16	0.56	0.56
Female Sexual Function*										
Overall	20	0.00	1.00	0.00	0.00	15	0.13	0.77	0.14	0.08
Surgical	12	0.33	0.54	0.42	0.18	10	0.20	0.71	0.24	0.12
Male Sexual Function										
Overall	52	0.31	0.34	0.13	0.13	34	0.41	0.27	0.18	0.19
Surgical	25	0.56	0.34	0.22	0.19	18	0.39	0.50	0.15	0.16
Palliative	7	0.29	0.63	0.13	0.19	5	0.20	0.85	0.11	0.09
Psychological Impact Scale										
Overall	85	-0.39	0.19	0.12	0.14	59	-0.53	0.14	0.16	0.19

Surgical	43	-0.70	0.11	0.21	0.25	33	-1.03	0.06	0.31	0.34
Palliative	14	0.07	0.93	0.02	0.02	10	-0.60	0.26	0.18	0.38
Healthcare Services Scale										
Overall	85	-0.71	0.00	0.38	0.33	59	-1.0	0.00	0.52	0.41
Surgical	43	-0.79	0.00	0.52	0.55	33	-1.27	0.01	0.81	0.51
Palliative	14	-0.57	0.21	0.26	0.36	10	-0.90	0.15	0.42	0.50

6.4 Discussion

The external validation analysis of the LRRC-QoL described in this chapter confirms the psychometric properties of the measure in an international cohort of patients. The LRRC-QoL demonstrated an excellent scale structure, acceptable reliability, excellent validity, and high responsiveness to clinical change. The strong results of the validity and responsiveness analyses particularly build on the findings described in chapter 4 of this thesis and demonstrate the ability of the LRRC-QoL measure to detect clinical change. This strongly supports its use as a disease-specific outcome measure of HrQoL in future clinical studies and trials.

The LRRC-QoL has previously undergone extensive testing of its scale structure and construct validity through multi-trait analysis, EFA, and repeat multi-trait analysis. Though the CFA was limited by the sample size, meaning the gender-specific Sexual Function scales could not be included, even with the addition of data from the original LRRC-QoL validation study, it demonstrated excellent fit of the measure's scale structure. The combination of analyses undertaken provide convincing evidence to confirm the construct validity of the LRRC-QoL. The results of the reliability analyses described in this chapter are perhaps less robust for some of the scales than those described in chapter 4. The lower results of the internal consistency for the Stoma, Urostomy, and Sexual Interest scales are likely to have been affected by small sample sizes and the high rate of missing data for item 19 regarding pain during sexual intercourse. Despite this, the majority of the scales demonstrated good reliability and temporal stability.

The LRRC-QoL demonstrated excellent convergent validity, confirming nearly all the a priori hypotheses regarding correlations with scales of the FACT-C and EORTC QLQ-CR29. The additional correlations identified were also clinically valid and further supported the convergent validity of the LRRC-QoL. The strong correlations between the Psychological Impact scale and the FACT-C Physical Well-Being and Functional Well-Being scales may reflect the impact of physical or functional limitations on patients' psychological state (299). Item GF4 "*I have accepted my illness*" in the FACT-C Functional Well-Being scale is likely to reflect similar underlying concepts as the items in the LRRC-QoL Psychological Impact scale regarding feeling uncertain about the future and worrying about possible future treatments. The LRRC-QoL also demonstrated its ability to discriminate between subsets of patients through known groups comparison. Female patients reported significantly worse psychological impact, previous studies exploring gender differences in patients with cancer have reported increased incidence of depression or depressive symptoms in female patients (300). Further investigation would be beneficial to explore this gender difference in the context of LRRC. Patients with lateral LRRC reported significantly worse lower limb symptoms. This corresponds directly to the anatomical pattern of disease, which frequently involves structures including the pelvic sidewall and sciatic nerve, resulting in lower limb symptoms. Patients with metastatic disease reported better healthcare experiences, this patient group are likely to require more investigations at baseline, which may result in them feeling more supported and reporting better experiences. Finally, patients undergoing pre-operative oncological treatment for LRRC reported worse stoma-related symptoms, this could relate to the impact of these treatments on stoma function, such as chemotherapy-induced diarrhoea (301). Overall, these results provide high quality evidence of the validity of the LRRC-QoL.

The confirmation that the LRRC-QoL is highly responsive to changes in clinical status over time has significant implications for future research, in which the LRRC-QoL could be used as a disease-specific outcome measure of HrQoL. In patients undergoing surgery with curative intent, overall HrQoL was demonstrated to worsen at 3-months, prior to improving slightly by 6-months. These findings echo those of previous studies in patients undergoing pelvic exenteration for LRRC, reporting HrQoL utilising the AQOL, SF-36 and FACT-C (98, 146). Patients undergoing surgery also reported worse pain at 3-months (p=0.06, ES 0.47, SRM 0.29). This has previously been identified as a significant issue affecting patients undergoing exenterative surgery for LRRC (164, 169), however, current reporting is limited by a lack of disease-specific measures to assess pain. This has now been addressed through the LRRC-QoL. Patients receiving surgical treatment also reported worse lower limb symptoms at both 3- (p=0.00, ES 1.00, SRM 0.58) and 6-months (p=0.00, ES 1.30, SRM 0.66), which has previously been identified in patients undergoing sacrectomy (100), or sciatic or femoral nerve resections (28). Scores for sexual interest were worse at 3-months (p=0.04, ES 0.32, SRM 0.37) prior to improving at 6-months, but not beyond baseline. Conversely, psychological impact was reported to be improved at 6-months (p=0.06, ES 0.31, SRM 0.34) in this patient group. These issues have not been explored extensively in patients undergoing surgery for LRRC and would benefit from further research. Interestingly, health care experiences were worse at both 3- (p=0.00, ES 0.52, SRM 0.55) and 6-months (p=0.01, ES 0.81, SRM 0.51) in this patient group, this has not previously been identified and will be further explored in the prospective cohort study described in chapter 7.

In relation to responsiveness of the LRRC-QoL in patients receiving treatment with palliative intent, overall HrQoL was significantly improved at 6-months (p=0.01, ES

0.37, SRM 1.11). As highlighted in chapter 4, HrQoL reporting in this specific subset of patients is sparse with somewhat mixed results (101, 164, 168). Notably, the existing evidence, including the current study, is limited by small numbers of patients receiving treatment with palliative intent. This is likely to continue to be the case in future studies given the challenges of recruiting this specific subgroup of patients (302). In relation to the LRRC-QoL scales, at 6-months patients receiving palliative treatment reported improved lower limb symptoms (p=0.03, ES 0.42, SRM 0.82) and stoma-related issues (p=0.02, ES 0.96, SRM 1.23).

The recruitment of a cohort including over 200 patients with LRRC across 13 countries is a landmark achievement: arguably representing the largest multinational study of HrQoL in LRRC to date. Despite this, the study did not meet its recruitment target, specifically to enable CFA testing in the external validation cohort. Given that some of the LRRC-QoL scales, namely the Stoma, Urostomy, and Sexual Function scales, are specific to subgroups of patients, a sample size of greater than 10 participants per item is likely to be required. This was evident given that it was not possible to assess all nine scales through CFA despite the combined cohort of over 320 patients. The known groups analysis was also limited by high rates of missing clinical data.

The low incidence of LRRC represented one of the most significant barriers to reaching the target sample size for this study. The challenges associated with evaluating the psychometric properties of PROMs in rare disease settings are recognised and have been highlighted in the ISPOR task force report, acknowledging that standard methods may not be feasible in this context (290). Alternatives include altering statistical approaches, through utilising nonparametric tests or using continuous variables, or recruiting patients

with similar diseases to expand the potential sample (290). These options were not felt to be appropriate or necessary in the current study, however other recommendations were adopted, including recruiting from major treatment centres, and using electronic and telephone data collection. Most crucially, a multinational recruitment strategy was employed, without which it would not have been possible to achieve a sufficient sample for the analyses described in this chapter. This approach is supported by the ISPOR recommendations (290), and through a combination of cross-cultural adaptation and external validation, has produced validated measures for use in 14 countries across five continents.

6.5 Conclusion

The results of this external validation analysis, in combination with the analysis described in chapter 4, demonstrate the excellent psychometric properties of the LRRC-QoL, confirming its status as the optimal PROM for reporting HrQoL in LRRC. Further prospective reporting utilising the LRRC-QoL will provide greater insight into the impact of LRRC on HrQoL and is explored further in chapter 7.

Chapter 7 Longitudinal Health-Related Quality of Life Outcomes in Locally Recurrent Rectal Cancer Reported by the LRRC-QoL

7.1 Introduction

Current prospective reporting of HrQoL in patients with LRRC is summarised in chapters 1 and 2 of this thesis, particularly from a methodological standing. In relation to outcomes reported following surgery for LRRC, HrQoL is generally reported to decrease 3-6 months post-surgery, before returning to baseline at around 12-months (28, 98-100). However, these outcomes have not been reported using measures validated in patients with LRRC. Additionally, there is very limited evidence regarding HrQoL in patients receiving palliative treatment (39). The cross-cultural adaptation and external validation of the LRRC-QoL measure, described in chapters 5 and 6, enables its utilisation on an international platform to prospectively assess HrQoL in patients with LRRC. This will engender better understanding of the impact of LRRC and its different treatment modalities on HrQoL through reporting internationally generalisable HrQoL outcomes using an appropriately developed and validated measure. The aim of this study was to report prospective HrQoL in LRRC utilising the LRRC-QoL from baseline diagnosis up to 12-months, and to compare HrQoL outcomes between subgroups of patients based on clinical and demographic variables.

7.2 Methods

A prospective cohort study with a 12-month period of follow-up was undertaken as described in workstream II, chapter 6. Only data up to the 6-month timepoint are reported in this study as follow-up was ongoing at the time of analysis. HrQoL was assessed using the LRRC-QoL at baseline, 3-, and 6-, and 12-months. The eligibility criteria are detailed in chapter 6. Recruitment to the study was undertaken at 18 centres in 5 countries including France, Italy, the Netherlands, New Zealand, and the UK. Recruitment strategies are described in more detail in chapters 9 and 10. The target sample size of the study was 320 patients, in keeping with the sample size for the external validation of the LRRC-QoL.

7.2.1 Data Analysis

Data were analysed using SPSS Statistics for Mac, version 26 (IBM Corp., Armonk, N.Y., USA) and R Statistical Software (v4.2.3; R Core Team 2023). A descriptive analysis was undertaken for demographic and clinical data. Data completeness for the LRRC-QoL was assessed at each timepoint at a questionnaire level and at an item and scale level for the completed questionnaires. Missing data were handled with multiple imputation when over 50% of the items in a scale were completed (273, 297), using the R mice package (v3.16.0; van Buuren and Groothuis-Oudshoorn, 2011) (295). Missing data at a scale level was defined as one or more items missing.

The LRRC-QoL is a disease-specific measure of HrQoL in LRRC, scoring instructions are described in chapter 6 and Appendix 6. Scores were calculated for each patient at each timepoint for overall HrQoL and each scale. A general linear model with adjustment for

baseline overall score was used to evaluate changes in HrQoL over time. This model accommodates the assessment of longitudinal data in patients with outcome data available at each timepoint. Comparisons between groups were planned for the following groups: gender, pattern of recurrence, treatment intent, presence of metastatic disease, pre-operative treatment for LRRC, LRRC resection margin, and type of palliative treatment. Due to an insufficient sample size, it was not possible to undertake all these analyses and only treatment intent was analysed. P values <0.05 were considered statistically significant, only the results for models meeting this threshold were reported. In order to understand better the clinical significance of the observed statistically significant changes overtime, we calculated changes in overall HrQoL scores at an individual patient level through subtracting baseline overall HrQoL score from scores at 3- and 6-months. The distributions of these change scores were then examined to understand what proportions of patients deteriorated, remained stable, or improved. This descriptive approach was undertaken, as the LRCC-QoL is a new instrument and there is no data on what change may be clinically meaningful.

7.3 Results

Recruitment to the study took place between November 2020 and July 2023. There were 101 patients recruited to the study who had reached 6-month follow-up by July 2023 and were included in the results reported in this chapter. It was not possible to include 12-month follow-up data due to the small number of patients who had reached this timepoint and were alive (n=59), of which 37 had responded by July 2023. Full 12-month follow-up for the overall cohort will be reported in due course, the results reported in this chapter therefore represent an interim analysis.

7.3.1 Patient Demographics and Clinical Characteristics

The patient demographics and clinical characteristics are described in Table 7.1. Participants were recruited from 18 sites across five countries, 69 (68.3%) patients were male, and the majority were of white ethnicity (n=87, 86.1%). Median age was 67.0 (IQR 13.0) and participants most commonly reported being retired (n=46, 45.5%), and a majority were married (n=56, 55.4%). The median interval between PRC and recurrence was 20.5 months (IQR 30.5) and was most commonly detected via surveillance (n=47, 46.5%). Patterns of recurrence were well represented, with anterior being the least commonly reported (n=8, 7.9%) and 12 (11.9%) participants had metastatic disease. Fifty-six (55.4%) participants received treatment with curative intent, of which 46 were reported to have undergone surgery at the time of analysis, with 32 (69.6%) undergoing a R0 resection. Eighteen of the patients undergoing surgery did not receive neoadjuvant treatment for LRRC (39.1%), whereas 28 (60.9%) did. Three patients received SABR with reported curative intent. Twenty (35.7%) received no pre-operative treatment and long course chemoradiotherapy was the most received form of pre-operative treatment for LRRC (n=22, 39.3%). A wide range of surgical procedures were performed for LRRC, Appendix 5 provides an overview for the entire workstream II cohort. There were missing data rates of up to 35.6% for clinical variables including PRC margin status and pattern of LRRC.

Table 7.1: Patient demographics and clinical characteristics

Variable	**Responders (n=101)**
Demographics (%)	
Country	
France	2 (2.0)

Italy	6 (5.9)
Netherlands	14 (13.9)
New Zealand	1 (1.0)
UK	78 (77.2)
Sex	
Male	69 (68.3)
Female	32 (31.7)
Median Age (IQR)	67.0 (13.0)
Ethnicity	
White	87 (86.1)
Black	2 (2.0)
Other	1 (1.0)
Unknown	11 (10.9)
Marital status	
Married	56 (55.4)
Civil partnership	1 (1.0)
Living with partner	4 (4.0)
Widowed	8 (7.9)
Separated	3 (3.0)
Divorced	5 (5.0)
Single	12 (11.9)
Other	1 (1.0)
Unknown	11 (10.9)
Education status	
Secondary school	38 (37.6)
College	15 (14.9)
University	20 (19.8)
Other	12 (11.9)
Unknown	16 (15.8)

Employment status	
Self-employed	11 (10.9)
Looking after family or home	2 (2.0)
Full time employment	9 (8.9)
Part time employment	5 (5.0)
Unemployed	7 (6.9)
Sick leave	8 (7.9)
Retired	46 (45.5)
Other	2 (2.0)
Unknown	11 (10.9)
Treatment for Primary Rectal Cancer (%)	
Location of PRC (distance from anal verge)	
High rectal (>10cm)	22 (21.8)
Mid rectal (5.1-10cm)	23 (22.8)
Low rectal (0-5cm)	26 (25.7)
Unknown	30 (29.7)
Neo-adjuvant Treatment	
None	37 (36.6)
SCRT	3 (3.0)
LCCRT	21 (20.8)
Chemotherapy	3 (3.0)
SCRT followed by chemotherapy	2 (2.0)
LCCRT followed by chemotherapy	2 (2.0)
Chemotherapy followed by LCCRT	4 (4.0)
Other	1 (1.0)
Unknown	28 (27.7)
Operation for PRC	
Local excision	6 (5.9)
Anterior resection	38 (37.6)
Abdominoperineal resection	17 (16.8)
Hartmann’s procedure	6 (5.9)
Other	7 (6.9)
Unknown	27 (26.7)

Margin status	
R0	54 (53.5)
R1	9 (8.9)
R2	2 (2.0)
Unknown	36 (35.6)
Adjuvant treatment	
None	43 (42.6)
Radiotherapy	1 (1.0)
Chemoradiotherapy	7 (6.9)
Chemotherapy	21 (20.8)
Unknown	29 (28.7)
Median interval between Primary and Recurrence in months (IQR)	20.5 (30.5)
Locally Recurrent Rectal Cancer (%)	
Mode of detection	
Symptomatic	23 (22.8)
Surveillance	47 (46.5)
Other	3 (3.0)
Unknown	28 (27.7)
Pattern of LRRC	
Anterior	8 (7.9)
Central	23 (22.8)
Lateral	14 (13.9)
Posterior	20 (19.8)
Unknown	36 (35.6)
Presence of Metastatic disease	
Yes	12 (11.9)
No	60 (59.4)
Indeterminate	1 (1.0)
Unknown	28 (27.7)
Number of Sites of Metastases	
1	12 (11.9)
2	1 (1.0)
N/A	60 (59.4)
Unknown	28 (27.7)
Sites of Metastases	
Liver	3 (3.0)
Lung	5 (5.0)

Other	4 (4.0)
Treatment Intent	
Curative	56 (55.4)
Palliative	18 (17.8)
Unknown	27 (26.7)
Curative Treatment for LRRC (n=56)	
Neoadjuvant treatment only to date	4 (7.1)
Neoadjuvant treatment followed by surgery	28 (50.0)
Surgery without neoadjuvant treatment	18 (32.1)
SABR	3 (5.4)
Unknown or no treatment yet	3 (5.4)
Pre-operative Treatment (n=56)	
None	20 (35.7)
SCRT	3 (5.4)
LCCRT	22 (39.3)
Chemotherapy	4 (7.1)
SCRT followed by chemotherapy	1 (1.8)
LCCRT followed by chemotherapy	1 (1.8)
Chemotherapy followed by SCRT	3 (5.4)
Chemotherapy and re-irradiation	1 (1.8)
Other	1 (1.8)
Margin Status following surgery (n=46)	
R0	32 (69.6)
R1	4 (8.7)
Unknown	10 (21.7)
Palliative Treatment (n=18)	
Chemotherapy	6 (33.3)
Radiotherapy	6 (33.3)
Chemoradiotherapy	3 (16.7)
Unknown	3 (16.7)

7.3.2 Data Completeness

At baseline, 101 patients were included in the study, with follow-up response rates of 77.3% (n=75) at 3-months, and 62.1% (n=59) at 6-months, as detailed in Figure 7.1.

There were attrition rates of 22.7% (n=22/97) at 3-months and 37.9% (n=36/95) at 5-months. Data completeness for the LRRC-QoL scales was high overall and is demonstrated in Table 7.2, data completeness for each item is included in Appendix 7. The Sexual Interest scale demonstrated high rates of missing data, particularly for item 19 regarding pain during sexual intercourse, which had missing data rates of 25.7% to 42.7%.

Figure 7.1: Recruitment and Follow-up

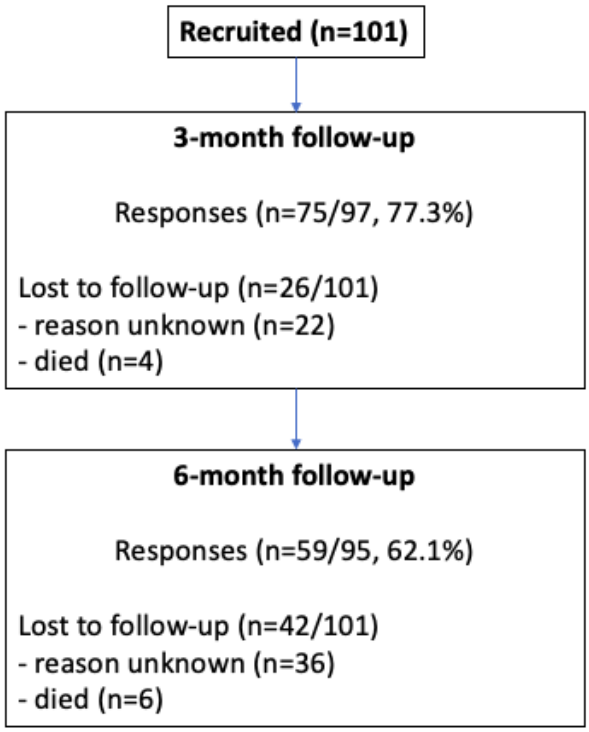


Table 7.2: Data completeness for the LRRC-QoL scales at each timepoint

	Baseline		**3-months**		**6-months**	
	N	**Missing (%)**	**N**	**Missing (%)**	**N**	**Missing (%)**
Pain Scale	101	1 (1.0)	75	2 (2.7)	59	0 (0.0)
Urinary Symptoms Scale	101	1 (1.0)	75	1 (1.3)	59	0 (0.0)
Lower Limb Symptoms Scale	101	1 (1.0)	75	0 (0.0)	59	0 (0.0)

Stoma Scale	67	5 (7.5)	64	5 (7.8)	50	5 (10.0)
Urostomy Scale	11	1 (9.1)	17	2 (11.8)	19	0 (0.0)
Sexual Interest Scale	101	26 (25.7)	75	32 (42.7)	59	25 (42.4)
Female Sexual Function Scale	32	3 (9.3)	19	2 (10.5)	17	2 (11.8)
Male Sexual Function Scale	69	5 (7.3)	56	16 (25.6)	42	9 (21.4)
Psychological Impact Scale	101	0 (0.0)	75	0 (0.0)	59	1 (1.7)
Healthcare Services Scale	101	0 (0.0)	75	1 (1.3)	59	0 (0.0)
Item 9 – bleeding or discharge from rectum	81	12 (14.8)	42	4 (9.5)	29	4 (13.8)
Item 10 – pain or discharge from wound(s) or scar(s)	101	23 (22.8)	75	17 (22.7)	59	9 (15.3)
Item 28 – worried about becoming dependent	101	0 (0.0)	75	0 (0.0)	59	0 (0.0)

7.3.3 HrQoL Outcomes

7.3.3.1 HrQoL Changes for the Overall Cohort

Fifty-four patients completed the LRRC-QoL at all three timepoints and were included in the general linear models for the overall cohort. It was not possible to compare HrQoL outcomes for all variables intended due to the small sample size of the overall cohort, therefore only outcomes by treatment intent are reported. These analyses will be undertaken once all patients have completed 12-month follow-up. Several changes in HrQoL over time were identified which are reported below, results for the general linear models which did not reach statistical significance are not reported. Table 7.3 demonstrates mean LRRC-QoL scores, including scales and individual items, for the overall cohort at each timepoint.

Table 7.3: Mean LRRC-QoL scores for the overall cohort at each timepoint

	Score range	Higher score denotes…	Baseline			3-months			6-months		
			N	Mean score	SD	N	Mean score	SD	N	Mean score	SD
Overall HrQoL Score	18-96	Worse HrQoL	101	36.85	9.10	75	37.52	9.49	59	38.53	10.72
Pain Scale	3-12	Worse pain	101	5.10	2.01	75	5.39	2.38	59	5.68	2.30
Urinary Symptoms Scale	2-8	Worse symptoms	101	2.89	1.35	75	2.88	1.18	59	2.76	1.21
Lower Limb Symptoms Scale	3-12	Worse symptoms	101	5.01	2.11	75	5.81	2.71	59	6.05	2.90
Stoma Scale	2-8	Worse symptoms	67	3.25	1.32	64	3.00	1.39	50	2.88	1.10
Urostomy Scale	3-12	Worse symptoms	11	4.73	1.56	17	4.76	2.02	19	5.26	1.97
Sexual Interest Scale	2-8	Higher sexual interest	101	2.66	1.09	75	2.19	1.13	59	2.28	1.20
Female Sexual Function Scale	2-8	Worse sexual function	32	2.68	1.22	19	2.56	1.25	17	2.73	1.39
Male Sexual Function Scale	2-8	Worse sexual function	69	4.97	2.33	56	5.00	2.24	42	5.46	2.45
Psychological Impact Scale	4-16	Worse psychological impact	101	10.04	3.34	75	9.47	3.12	59	9.59	3.58
Healthcare Services Scale	3-12	Better healthcare experiences	101	10.40	2.00	75	9.80	2.09	59	9.41	2.21
Item 9 – bleeding or discharge from rectum	0-4	Worse symptoms	81	1.61	0.77	42	1.63	0.82	29	1.62	0.90

Item 10 – pain or discharge from wound(s) or scar(s)	1-4	Worse symptoms	101	1.26	0.57	75	1.59	0.92	59	1.46	0.76
Item 28 – worried about becoming dependent	1-4	Worse symptoms	101	2.58	1.07	75	2.37	1.01	59	2.36	1.08

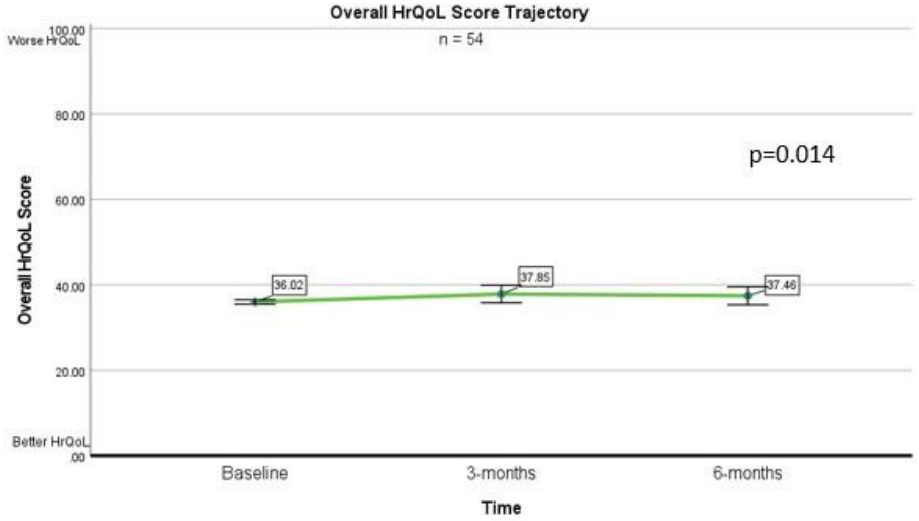
Regarding overall HrQoL, mean scores for the entire cohort were 36.85 at baseline, 37.52 at 3-months, and 38.53 at 6-months (see Table 7.3), with an increase in score indicating worse HrQoL. The general linear model of 54 patients demonstrated similar results, illustrating stability over time, with a significant p value of 0.014. The adjusted means from the general linear model results for the overall cohort are demonstrated in Figure 7.2.

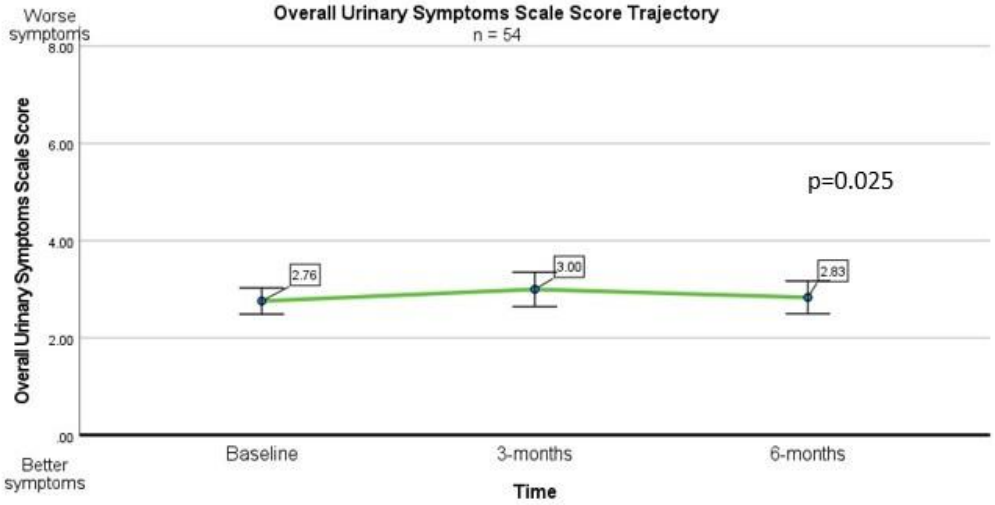
In relation to the LRRC-QoL scales, Pain scores for the overall cohort increased to a small degree over time, with higher scores denoting worse pain; mean score of 5.10 at baseline, 5.39 at 3-months, and 5.68 at 6-months. Lower Limb Symptoms mean scale scores also worsened over time, from a baseline of 5.01, to 5.81 at 3-months, and 6.05 at 6-months. Mean overall Stoma scale scores improved over time from a baseline of 3.25, to 3.00 at 3-months, and 2.88 at 6-months, with lower scores indicating lower burden of stoma-related issues. Conversely, mean Urostomy scale scores worsened slightly over time, from a baseline mean score of 4.73, to 4.76 at 3-months, and 5.26 at 6-months. Overall Sexual Interest scale scores were slightly reduced, indicating lower sexual interest, with a mean score of 2.28 at 6-months from a baseline of 2.66, though this scale had high rates of missing data at all timepoints. Regarding sexual function, mean scale scores were relatively stable across all timepoints in female patients but increased slightly in male patients, indicating worsening function, from 4.97 at baseline, 5.00 at 3-months, to 5.46 at 6-months. None of these changes were statistically significant.

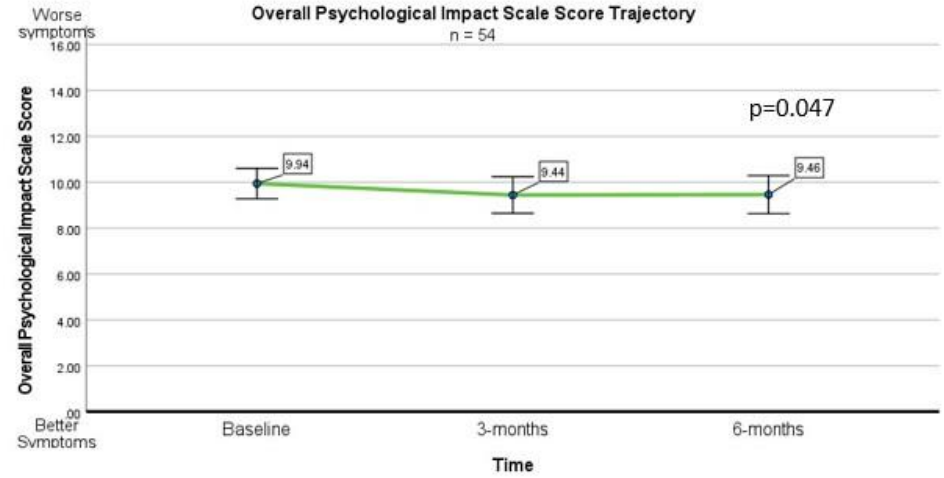
Statistically significant differences were identified in general linear models for three of the LRRC-QoL scales and are demonstrated in Figure 7.2. Mean Urinary Symptoms scale scores for the overall cohort were 2.89 at baseline, 2.88 at 3-months, and 2.76 at 6-

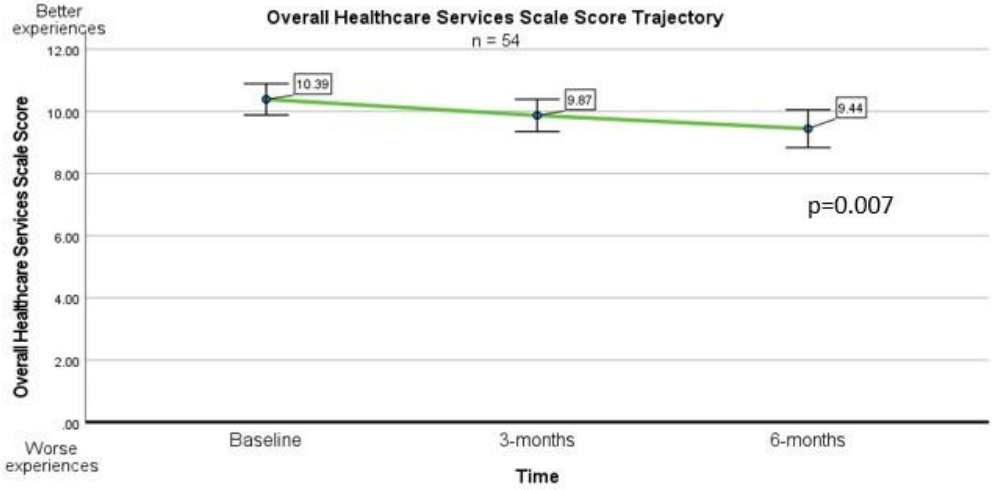
months, with a higher score denoting worse symptoms. Regarding the general linear model, Urinary Symptoms scale scores were highest at 3-months, with a p value of 0.025. The overall cohort of patients reported mean Psychological Impact scale scores of 10.04 at baseline, 9.47 at 3-months, and 9.59 at 6-months, with higher scores representing worse symptoms. The general linear model of 54 patients demonstrated a similar trend, with a p value of 0.047. Mean scores for the Healthcare Services scale in the overall cohort were 10.40 at baseline, 9.80 at 3-months, and 9.41 at 6-months, higher scores indicate better experiences. The general linear model also demonstrated a deterioration in scale scores over time, with a p value of 0.007.

Figure 7.2: General linear models for the overall cohort





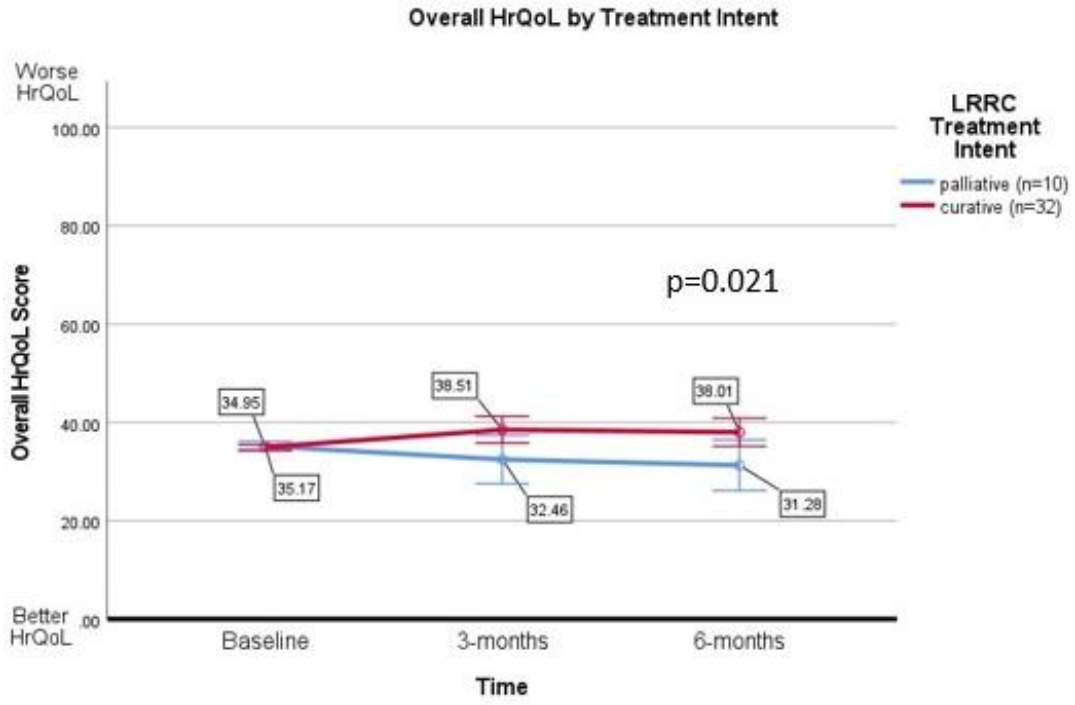




7.3.3.1.1 Treatment Intent

Overall HrQoL scores were compared by treatment intent, with the general linear model illustrated in Figure 7.3. Scale scores at all three timepoints were available for 10 patients receiving treatment with palliative intent and 32 patients receiving treatment with curative intent and were included in the model. Mean overall HrQoL scores were 35.17 in the palliative group at baseline, 32.46 at 3-months, and 31.28 at 6-months, higher scores representing worse overall HrQoL. Compared with 34.95 at baseline, 38.51 at 3-months, and 38.01 at 6-months in the curative group, with a p value of 0.021. No other statistically significant differences were observed for the LRRC-QoL scales except for the Lower Limb Symptoms scale, with a p value of 0.010. For this scale, scores in the palliative group were 5.71 at baseline, 5.36 at 3-months, and 4.73 at 6-months, with higher scores denoting worse symptoms. In the curative treatment patient group, mean scores were 4.34 at baseline, 6.04 at 3-months, and 5.99 at 6-months.

Figure 7.3: General linear model of overall HrQoL by treatment intent



7.3.3.2 HrQoL Changes at an Individual Patient Level

Changes in overall HrQoL scores were evaluated at an individual patient level at 3- and 6-months. Mean change at 3-months was 2.28 (SD 7.99), as demonstrated in Figure 7.4, with 23 (30.7%) patients reporting an increase in score of ≥5. An increase in score denotes worse overall HrQoL. Mean change at 6-months was 1.81 (SD 7.74), as demonstrated in Figure 7.5, with 19 (32.2%) patients reporting an increase in score of ≥5.

Figure 7.4: Distribution of overall HrQoL change scores at 3-months

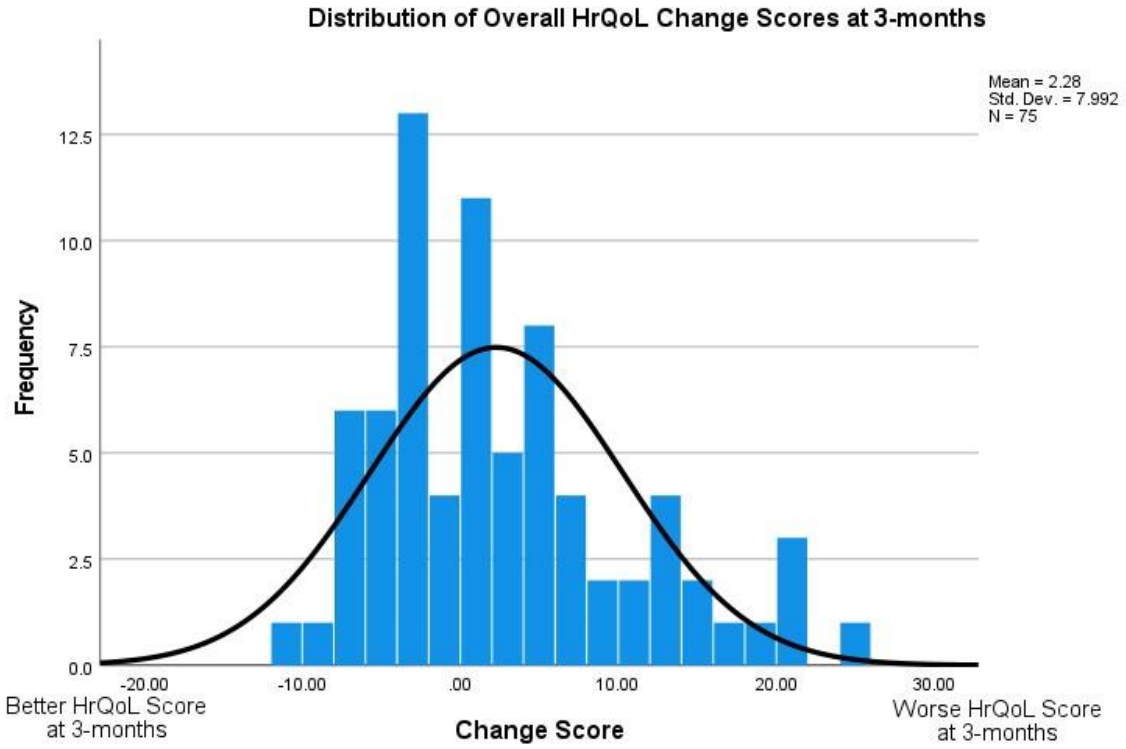
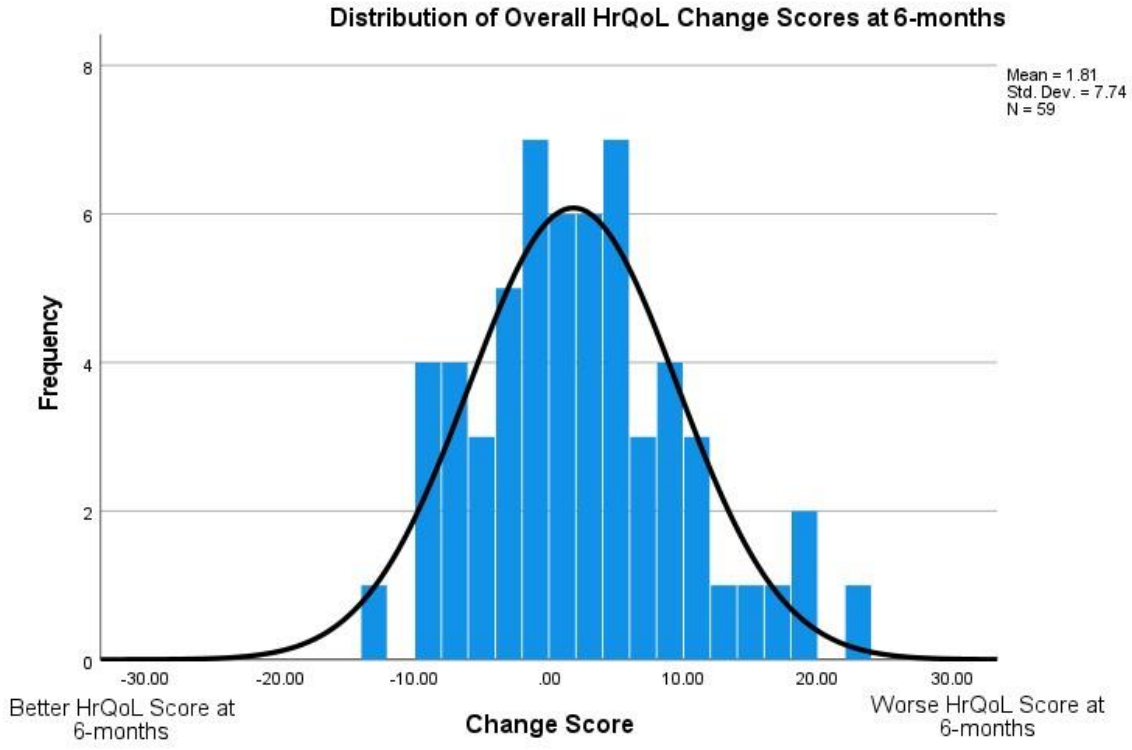


Figure 7.5: Distribution of overall HrQoL change score at 6-months



7.4 Discussion

This study is the first to report HrQoL in LRRC utilising an appropriately validated, disease-specific measure and has identified several significant outcomes with important clinical implications. The findings suggest that overall HrQoL is relatively stable from baseline to 6-months in patients with LRRC. Though change scores at an individual patient level suggest that overall HrQoL deteriorates for a significant proportion of patients. Trends in HrQoL were observed through changes in mean scores for the overall cohort, with reported pain, lower limb symptoms, urostomy or urinary-device related issues, and male sexual function worsening over the study period, whilst stoma-related issues improved over 6-months. Statistically significant differences were identified through general linear models for three of the LRRC-QoL scales, with worse urinary symptoms at 3-months, whereas psychological impact was improved from baseline at both 3- and 6-months. Healthcare experiences for the overall cohort worsened over time.

The results of the study demonstrate clear differences in overall HrQoL between patients receiving curative treatment and palliative treatment. Patients receiving treatment with curative intent reported worse HrQoL at both 3- and 6-months, whereas reported HrQoL steadily improved from baseline in patients receiving palliative treatment during this time. These results expand on the published literature regarding HrQoL in LRRC, providing a disease-specific focus in capturing the range of HrQoL issues relevant to this patient group utilising a single PROM. This includes HrQoL domains which are not captured in generic or colorectal cancer-specific PROMs, such as urostomy-related issues, issues related to wounds or scars, or lower limb symptoms including leg weakness or paraesthesia. Potentially providing a more comprehensive reflection of overall HrQoL differences between these patients. The improvement observed in the palliative treatment

group is an important and arguably reassuring finding, given that providing symptom relief and improving HrQoL, are central aims of palliative care (303). Though these results are limited by the small sample size of ten patients, they contribute to the small evidence base regarding HrQoL in this context. It is also crucial that these findings are considered alongside survival outcomes; notably, four of the six patients who died prior to 6-month follow-up received treatment with palliative intent. The palliative treatments reported in the study included chemotherapy, radiotherapy, or a combination of both, for which reported overall median survival is around 15 months (54). The full 12-month study data will provide further insight regarding whether the improvement in overall HrQoL provided by palliative treatment continues beyond 6-months in a larger sample of patients.

The stability in HrQoL scores over time for the overall cohort is likely to reflect the heterogeneity of the patients included in the study, particularly given that clear differences were demonstrated in relation to treatment intent. However, there were within group differences regarding treatment and outcomes were not compared in relation to specific treatments. The curative patient group included patients who had only received neoadjuvant treatment for LRRC to date (n=4, 7.1%), patients who had received pre-operative oncological treatments followed by surgery (n=28, 50.0%), patients who had proceeded straight to surgery (n=18, 32.1%), and patients who had received SABR with reported curative intent (n=3, 5.4%). Patients receiving pre-operative treatments such as radiotherapy or SABR with curative intent may have experienced either stability or improvement in their symptoms in relation to tumour regression, as previously demonstrated in a palliative setting (168). The overall deterioration in HrQoL in patients receiving treatment with curative intent is likely to reflect the negative impact of pelvic exenteration surgery, which has previously been reported across a range of pelvic

malignancies, including LRRC (12, 28, 98, 100, 146, 147, 164, 167, 169, 171, 173, 181, 304-306). The distribution of HrQoL change scores at an individual patient level for the overall cohort suggest that around a third of patients reported deterioration in their HrQoL to a relatively large magnitude, with increases in scores of greater than 5. As the LRRC-QoL is a new instrument, there is no data on what change may be clinically meaningful. Therefore, we decided to descriptively examine the distribution of the changes scores to gain better understanding of the trajectory of HrQoL for individuals. I chose to report 5 points as a change because similar change scores were reported as MIDs for the EORTC QLQ-C30 in patients with advanced colorectal cancer (307). However, future research will be required for formal evaluation of MIDs for the LRRC-QoL and its scales, in order to facilitate clinical interpretation of group level changes and differences. Overall, the results suggest that HrQoL, as measured by the LRRC-QoL, deteriorates from baseline in patients receiving treatment with curative intent, in keeping with outcomes previously reported in this patient group (98). No significant differences in outcomes by treatment intent were identified for the LRRC-QoL scales, with the exception of lower limb symptoms, which were worse in patients receiving curative treatment. These findings reflect physical function outcomes previously reported in patients undergoing pelvic exenteration, particularly in patients with disease involving the pelvic sidewall or sacrum (99).

In contrast to the results described in this chapter, previous prospective studies have reported worse HrQoL outcomes in patients receiving treatment with palliative intent (98, 164). Choy et al.'s study compared a cohort of 93 patients undergoing surgery to 24 patients receiving treatment with palliative intent, utilising the AQOL measure (98). Patients receiving treatment with palliative intent reported a gradual decline in HrQoL over 12-months (98). Similarly, You et al.'s comparison of FACT-C scores in 62 patients

undergoing curative treatment for LRRC and 43 patients receiving non-curative treatments, demonstrated a significant deterioration in physical wellbeing scores in patients receiving non-curative treatment (164). Notably, both studies included a proportion of patients undergoing surgery within the palliative treatment group (n=16, 23.9%), in addition to patients receiving best supportive care (n=13, 19.4%) (98, 164). Both factors could contribute to the observed deterioration in HrQoL; palliative surgery has previously been associated with worse HrQoL outcomes in patients with LRRC (101). Furthermore, they report outcomes only in patients referred to highly specialist surgical centres in Australia and the USA (98, 164), meaning this subgroup of patients are not necessarily representative of all patients receiving palliative treatment, as a significant proportion may not have been referred to these centres (308). Conversely, the study described in this thesis includes patients recruited from 18 sites with a range of referral volumes, and the palliative treatment group did not include patients undergoing surgery or best supportive care.

An important additional factor to consider, as previously highlighted, is the utilisation of a disease-specific measure in the LRRC-QoL. A previous cross-sectional study of short-term HrQoL outcomes in LRRC identified a lower burden of pelvic symptoms, including urinary frequency and frequency of defaecation, as assessed by the EORTC QLQ-CR29, in patients receiving palliative treatment (102). Though overall HrQoL, assessed utilising the FACT-C, was better in patients undergoing curative surgery (102). The LRRC-QoL has an even greater focus on pelvic symptoms than either of these measures, including items assessing urinary symptoms, pelvic and buttock pain, discharge from the rectum, and sexual function. The ability to capture these symptoms may explain why an improvement in HrQoL in the palliative setting was identified in this study. These issues

are not captured to the same extent in other PROMs which have been used extensively in this setting (see chapter 2), meaning they may not necessarily elicit these differences.

Differences identified in LRRC-QoL scale scores for the overall cohort included worse psychological impact at baseline, followed by improvement at both timepoints. This is consistent with previous studies in LRRC, reporting improved mental component scores, as assessed utilising the SF-36, at 6-months (32, 165). This is also reported to be the case generally in patients undergoing pelvic exenteration (99). Interestingly, patients with LRRC have been reported to have better baseline mental component scores when compared with other disease groups (32, 165).

A significant finding was the worsening of reported healthcare experiences for the overall cohort at both 3- and 6-months. The impact of negative treatment effects on patient's overall HrQoL may have contributed to these results. A previous study in Irish colorectal cancer survivors found that lower levels of satisfaction with continuity of care were associated with worse overall HrQoL, assessed utilising the FACT-C (309). It is possible that this association may be particularly relevant in patients with LRRC, given the complex and radical nature of its treatment and associated high levels of morbidity. The study also took place during and in the aftermath of the COVID-19 pandemic, which may have negatively affected patient's healthcare experiences. Item 31 regarding satisfaction with the speed of implementing tests and/or treatment, demonstrated the worst mean scores from the overall scale components, with a mean score of 3.29 at baseline, 3.18 at 3-months, and 2.97 at 6-months (see Appendix 7). This may reflect increased waiting and referral times during recent years across numerous healthcare settings, including the NHS (310-312). To our knowledge, prospective reporting of healthcare experiences in LRRC

has not been undertaken to date to enable comparison. However, healthcare experiences of patients with advanced or recurrent colorectal cancer have been explored through a qualitative study from a survivorship perspective, with the findings reflecting the complex and nuanced nature of these experiences (144). The negative issues identified in the study relating to the acute care period may be reflected in the worsening Healthcare Services scores, and included poor communication, feeling excluded from decision-making, and barriers to reporting side effects, such as limited appointment times (144).

The study has several strengths, the most significant being its utilisation of a disease-specific measure to examine the impact of LRRC and its treatment on HrQoL, building considerably on the existing evidence in this field. The LRRC-QoL, as a disease-specific measure, is likely to be more sensitive in identifying differences in HrQoL outcomes. This is supported by the high levels of responsiveness to clinical change identified in the external validation study described in chapter 6. The follow-up rates at each timepoint were relatively good considering the challenging nature of recruiting to research studies in this setting, with response rates of 77.3% at 3-months and 62.1% at 6-months. Comparing favourably with previous studies in LRRC co-ordinated from a highly specialist referral centre, reporting a follow-up response rate of 72.1% at 6-months (165). A range of strategies were employed during the study to maintain these rates, which are described further in chapter 10. A major limitation is the small longitudinal sample size, despite maintaining high follow-up response rates, and the lack of 12-month HrQoL outcomes, which will be addressed in future work. The high rates of missing data for some clinical variables may also have impacted on the study results and limited the ability to compare outcomes in patients undergoing R0 resection, which has previously been associated with better HrQoL (102, 165, 171, 180). The LRRC-QoL was designed to be used in a modular approach alongside the EORTC QLQ-C30, however the core module

was not administered at the follow-up timepoints, which is a limitation of this work. Overall, the study results should be interpreted with caution given significant limitations related to the statistical analysis, including multiple testing and a small sample size, particularly for patients with data available at all timepoints. These limitations are associated with an increased risk of type I errors and further analysis in the full 12-month cohort would be beneficial to confirm these findings. Additionally, as previously highlighted, MIDs have not yet been established for the LRRC-QoL and will provide further insight from a patient-centred perspective when considered alongside more traditional statistical testing. Finally, the patients included in this analysis do not represent the full range of languages and countries in which the LRRC-QoL has been cross-culturally adapted (see chapter 5). The final 12-month dataset will also address this, improving the generalisability of this outcome data.

This study represents an important transition point in prospective reporting of HrQoL in LRRC, being the first to utilise a disease-specific, appropriately validated measure. The generation of high-quality HrQoL data is essential to enable inclusion of these outcomes within shared decision-making processes regarding patient care. This is particularly pertinent in this complex disease setting. Though the ability to utilise the study findings in clinical practice is currently constrained by the small sample size and incomplete study follow-up, these limitations will be addressed in future work. This will include reporting the full 12-month study data in a larger sample of patients, as recruitment to this study is due to complete in December 2023.

Regarding future research utilising the LRRC-QoL, presentation of HrQoL outcome data is an important consideration. Effectively communicating complex HrQoL outcome data

to patients can be challenging due to its requirement to be accessible across all levels of education. Tolbert et al. have previously investigated optimum formats for communicating HrQoL outcomes to patients visually through line graphs, establishing that line graphs of mean scores in which higher scores indicated “better” HrQoL were more accurately interpreted (313). The utilisation of simple line graphs has been deployed effectively in a recent systematic review of HrQoL following pelvic exenteration to facilitate patient decision making (99). Line graphs such as those included in this chapter could also be utilised for this purpose if adapted and simplified in keeping with Tolbert et al.’s findings (313). Further work with patient and public involvement groups could also be undertaken to explore approaches to communicating HrQoL information specifically in the context of LRRC.

Adoption of the LRRC-QoL across all studies reporting HrQoL in LRRC will enable better comparison of outcomes, something which is currently limited by the wide range of PROMs being used for this purpose, as highlighted in chapter 2. Utilising this data to establish MIDs for the LRRC-QoL and its scales will also facilitate interpretation of this outcome data from a clinically meaningful perspective. The data collected in this study could also be used to explore predictors of HrQoL, as previously reported by Choy et al. (98). Their study identified baseline HrQoL as a strong predictor of HrQoL at 12-months, with female gender and bony resection being associated with worse 12-month outcomes (98). Evaluation of these predictors will only be possible once 12-month follow-up is complete and reporting 12-month outcomes would add value to the HrQoL trajectories identified in this work. Following on from this, reporting longer-term HrQoL following diagnosis with LRRC, during treatment, and beyond, will enable greater understanding of the long-term impact of LRRC and its treatment on patients. Chapter 8 of this thesis

will explore this from a qualitative perspective and in the future, prospective, long-term HrQoL reporting utilising the LRRC-QoL could build on this work.

7.5 Conclusion

This study marks an important landmark in utilising the LRRC-QoL measure to report prospective HrQoL outcomes in LRRC. The results confirm those of previous studies, with worse HrQoL reported at 3- and 6-months in patients undergoing treatment with curative intent and better outcomes reported in the palliative treatment group. Psychological impact improved over time for the overall cohort of patients, whereas healthcare experiences deteriorated. These results could be used to inform clinical practice and incorporated within shared decision-making discussions with patients regarding their treatment for LRRC once full 12-month follow-up data is available.

Chapter 8 A Qualitative Study of Survivorship Issues in Long-Term Survivors of Locally Recurrent Rectal Cancer

8.1 Introduction

Survivorship issues following LRRC are relatively poorly documented, which is unsurprising given the historically low numbers of survivors. Chapter 1 of this thesis highlights several survivorship issues reported in patients with primary colorectal cancer, in addition to increasing evidence regarding survivorship in patients with LRRC up to 2 years following diagnosis or surgical resection. The survivorship issues previously described in these patient groups include post-surgical complications, reduced mobility, bowel dysfunction, stoma-related issues, issues related to chemotherapy such as peripheral neuropathy and fatigue, sexual dysfunction, negative body image, and changes in personal identity (135-138, 143). In addition to unmet needs including psychological and social support and a lack of information related to chronic complications of treatment (140, 141, 143, 144). However, these issues may not be as relevant to longer-term survivors. Curative surgical treatment strategies in LRRC are radical and individualised, with a view to achieving a R0 resection given its association with improved survival (19, 35). Chronic complications of exenterative surgery include impaired mobility and foot drop following sciatic nerve resection (28), empty pelvis syndrome (149), and urological complications (149). The effect of these issues on HrQoL and other experiences of long-term LRRC survivors remain underreported in the literature to date.

Understanding of cancer survivorship is increasing, recognising that HrQoL measures developed for patients undergoing treatment may not reflect the experiences of patients

following completion of treatment and beyond (119). For this reason, the measures used to assess HrQoL may not be appropriate for use in longer-term survivors, as it is assumed that they are unlikely to meet content validity criteria in this context. Identifying these issues can help inform decisions regarding HrQoL assessment in these groups of patients. This recognition led to the development of the EORTC survivorship modules, including a colorectal module, to assess HrQoL in these groups of patients (119, 134). However, as demonstrated in chapter 2 of this thesis, measures developed for patients with primary colorectal cancer, do not necessarily capture the range of issues experienced by patients with LRRC. Identifying long-term survivorship issues relevant to specific patient groups can be used to inform shared decision-making processes between patients and clinicians regarding treatment strategies and potential late and lasting effects from cancer and its treatment. Knowledge of survivorship issues can be used to inform survivorship care, particularly through the identification of issues or needs, which are not being met in current follow-up care pathways. This information could also be used to determine whether existing PROMs can be used to assess HrQoL in long-term survivors of LRRC.

8.1.1 Aims and Objectives

The aims of the study were:

- To identify the survivorship issues relevant to patients who have been treated for LRRC and have remained disease-free for 3 years or longer,
- To compare the survivorship issues identified in different groups of LRRC survivors (pattern of LRRC, oncological treatments received, country recruited from),

- To map the survivorship issues identified to the LRRC-QoL and EORTC SURV100 measures,
- To assess HrQoL in LRRC survivors using the LRRC-QoL measure.

8.2 Methods

A mixed-methods study was undertaken, including semi-structured qualitative interviews to identify survivorship issues and quantitative assessment of HrQoL utilising the LRRC-QoL. Recruitment was conducted at four centres in the UK, two centres in Australia, and one centre in Sweden, New Zealand, Denmark, Canada, and the Netherlands respectively. The study was approved by the West of Scotland REC 3 (ref 20/WS/0116) with additional ethical approvals at each participating international centre. This study is reported in keeping with Standards for Reporting Qualitative Research (SRQR) (314).

8.2.1 Eligibility Criteria

Patients were invited to participate in the study if the following criteria were fulfilled:

- aged ≥ 18 years,
- treated for LRRC more than 3 years ago and are disease-free,
- able to provide informed written consent to participate and,
- able to read and write in the target language.

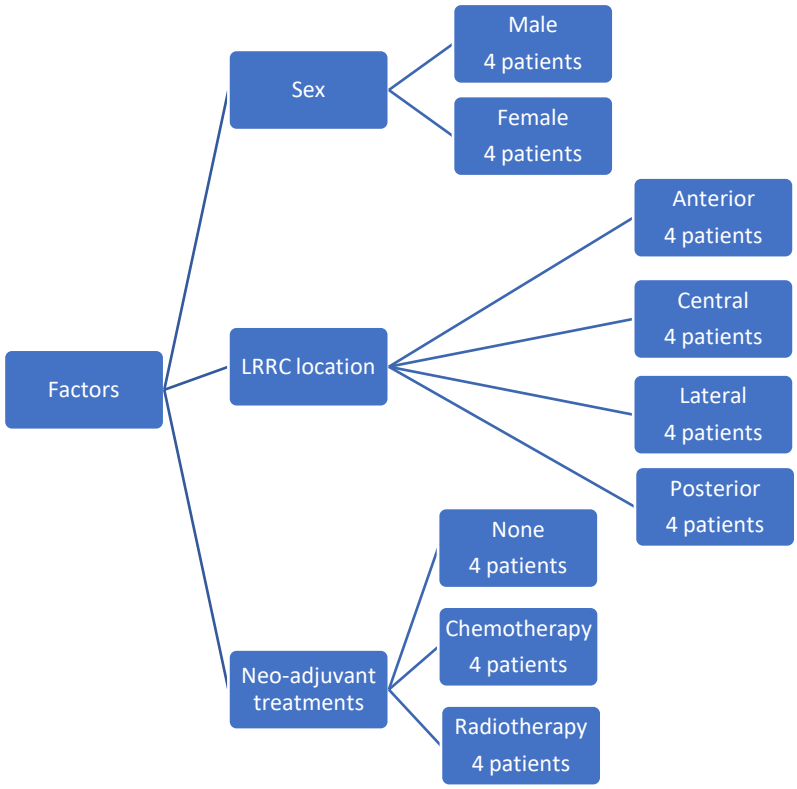
The exclusion criteria were as follows:

- patients with cognitive impairment,
- patients who have been treated for LRRC within the last 3 years,

- patients with a diagnosis of distant metastases (i.e., lung, liver) or locally re-recurrent rectal cancer following previous treatment for LRRC.

A purposive recruitment strategy was employed to recruit patients reflecting the diversity of LRRC survivors. A minimum of four patients per key factor were recruited, these factors are shown in Figure 8.1.

Figure 8.1: Purposive recruitment strategy



8.2.2 Data Collection

Specialist centres with experience in treating patients with advanced and recurrent pelvic malignancy were invited to participate in the study. International centres were included in the study to ensure that the study results were generalisable across different healthcare

systems. This also increased the number of potential participants which was an important consideration given the relatively rare nature of LRRC. Research teams at international centres with experience in conducting qualitative research were approached, given that researchers would be required to facilitate interviews at non-English-speaking sites. Recruitment to the study took place between November 2020 and July 2023. Ten centres participated in the study:

- St. Mark's Hospital, Harrow, UK,
- St. James's University Hospital, Leeds, UK,
- Leicester Royal Infirmary, UK,
- University Hospitals Birmingham, UK,
- Sahlgrenska University Hospital, Sweden,
- Christchurch Hospital, New Zealand,
- Aarhus University Hospital, Denmark,
- St. Paul's Hospital Providence Health, Vancouver, Canada,
- Erasmus MC Cancer Institute, Rotterdam, the Netherlands,
- Royal Adelaide Hospital. Australia,
- Peter MacCallum Cancer Centre, Melbourne, Australia.

Participants were identified by clinical teams at participating centres from existing registers of patients who had undergone surgical resection for LRRC with curative intent. Initially, patients in the UK were contacted via post with an information pack regarding the study, including a short patient information leaflet and a form to consent to their contact details being shared with the researcher. The researcher would then send them a participation pack via post including a patient information leaflet, a consent form and a demographics form to complete and return to the researcher via post using a self-

addressed, stamped envelope provided. The researcher would also contact potential participants via telephone to discuss the study and to arrange an interview. Recruitment using this two-stage approach was slow and a study amendment was implemented in March 2021, this process is described in more detail in chapters 9 and 10 of this thesis. The new approach involved participating teams at sites contacting potential participants via post with a participation pack. This included a letter inviting them to participate in the study, a patient information leaflet, a consent form, and a demographics form to complete and return to the researcher via post using a self-addressed, stamped envelope provided. In terms of the international recruitment process, patients were approached by a research team either in clinic or via telephone and provided with an information leaflet regarding the study, if they were happy to take part, they were then asked to complete a consent form and demographics form prior to arranging an interview.

The demographic data collected using the self-complete form were:

- Patient age,
- Patient sex,
- Ethnicity,
- Marital status,
- Education status,
- Employment status.

The consent form for the study included a clause for consent to the sharing of clinical data with the research team and following participants being recruited to the study, data were collected from their clinical team:

- Date of diagnosis with LRRC,

- Mode of detection of LRRC,
- Pattern of LRRC,
- Pre-operative treatment,
- Operation performed for LRRC,
- Date of surgery for LRRC,
- Margin status,
- Post-operative treatment.

Upon completion of the interview, participants were asked if they would be happy to receive the LRRC-QoL questionnaire via post or email link to complete and return to the research team, either using a self-addressed, stamped envelope or via REDCap.

8.2.3 Qualitative Interviews

Individual qualitative, in-depth, semi-structured interviews were undertaken using an interview topic guide (see Appendix 8), with open questions to identify survivorship issues relevant to patients who remain disease-free following treatment for LRRC. The LRRC-QoL conceptual framework was used to inform the topic guide with additional questions to explore the participants' lived experiences following treatment and during follow-up care. The LRRC-QoL conceptual framework was developed specifically for patients up to 2 years following diagnosis, for this reason, longer term survivors were considered to be at least 3-years post-treatment.

Interviews were facilitated by researchers who were native speakers of the same language as the participant; NM (English), SW and EG (Swedish), HvT (Danish) and JvR (Dutch). This approach was selected for several reasons, including the ability to better capture

culturally sensitive issues and linguistic idiosyncrasies when using native speakers as facilitators. Additionally, there were concerns that utilising a translator may influence the study results (315). For instance, the presence of a translator is a potential barrier to discussing sensitive or personal topics, it could also limit the building of rapport between interview facilitator and participant. From a practical perspective, due to the pandemic, it was not possible for the English-speaking researcher (NM) to travel to the international sites to facilitate interviews utilising a translator face-to-face. Conducting remote interviews using a translator was not considered to be feasible or appropriate by either the central research team or international sites. There were significant concerns that participants would not feel comfortable being interviewed remotely by an international researcher (NM) using a translator. From a feasibility perspective, co-ordinating remote interviews across different time zones and languages, involving the facilitator (NM), translator, local research team, and participant, would have been challenging.

All interview facilitators had either received training in qualitative methodology or were experienced qualitative researchers. Interviews were undertaken either via telephone, Microsoft Teams, or in person. The researcher explained the aim of the interview and his or her own background prior to commencing the interview. Participants were also informed that they could terminate the interview at any point should they wish to. Each interview was audio-recorded and transcribed verbatim immediately following the interview by the interview facilitator, the transcriptions included any concurrent notes made during the interview. The recordings were transcribed verbatim and pauses, emphasised words, expression of emotion and unintelligible speech were included in the transcription. Conversational norms such as interruptions and overlapping speech were also preserved.

8.2.4 Data Analysis

8.2.4.1 Qualitative Analysis

A framework approach to thematic analysis was used (316-318). This approach was felt to be suited to the aim of the study to identify survivorship issues relevant to a group of patients who had all undergone surgical resection for LRRC, with the anticipation that there would be similarities in their experiences. Transcripts were analysed and coded sequentially following three interviews. This approach to thematic analysis was undertaken to enable collaborative working and the co-ordination of the study at multiple international sites, with recruitment underway simultaneously. Transcripts in Swedish were analysed in their original form, with the coding and quotations being translated into English by the researchers who undertook the interview (SW and EG) to enable their inclusion in the study results. This approach was taken for the Swedish site given that the researchers had capacity to undertake the analysis and meet regularly with the central researcher (NM) to continually review and update the analytic framework. Interview transcripts in Dutch and Danish were translated into English by professional translators, approved by the University of Leeds, to enable analysis by the researcher (NM). This approach was taken to reduce the burden on the researchers at these sites who had limited capacity to undertake the analysis and associated regular meetings. It also enabled the central researcher (NM) to have greater oversight of the analytic process and raw data. Prior to the analysis, the translated Dutch and Danish transcripts were reviewed by the researcher who undertook the interview to ensure conceptual equivalence was maintained through translation (315).

The first step in the analysis process was familiarisation with the interview transcript which was achieved through repeated readings. The transcripts were imported into NVivo 12 and coded line by line, with a code being a label assigned to describe data. A combined

inductive-deductive approach was used; coding was not pre-determined prior to commencing the analysis, however the identification of codes and themes was informed by the development of the LRRC-QoL conceptual framework (106). A matrix was developed with rows consisting of the cases (each participant) and columns for the codes identified from the data, this was reviewed and updated iteratively following the analysis and coding of the interviews. The matrix was interpreted to recognise patterns in the data; building a working analytic framework, themes were identified through grouping categories of codes which reflect similar or related concepts. During the development of the framework, a subset of transcripts was reviewed by a second researcher (NR). The working framework and coding were then applied to subsequent interviews. Throughout this process, the researcher (NM) went backwards and forwards between the transcripts and the codes and categories identified to further refine the analytic framework. In addition to holding regular meetings with the Swedish team (SW and EG) during the analysis of the Swedish interviews to discuss any proposed changes to the framework and ensure agreement. Recruitment to the study continued until no new themes were identified and thematic saturation was reached (319), in the context of this study, the approach was taken that no new themes were identified following two sequential sets of three interviews.

8.2.4.2 Comparative Thematic Analysis

A comparative analysis was undertaken to compare the survivorship issues identified in sub-groups of participants; the variables compared were selected given their association with differences in HrQoL outcomes in patients with LRRC (98, 165). These included gender and margin status. Comparative analyses regarding pattern of disease, surgical versus non-surgical treatment, age, and country were also undertaken.

8.2.4.3 Analysis of HrQoL Data

HrQoL data were obtained by sending the LRRC-QoL to participants following the qualitative interview either by post or email link to complete via REDCap. Data completeness was assessed, summary scores were calculated for each patient, and mean scores for the overall LRRC-QoL and each scale were calculated. Higher scores in the HrQoL scales (Pain, Urinary Symptoms, Lower Limb Symptoms, Stoma, Urostomy, Sexual Interest, Sexual Function, Psychological Impact) indicate worse HrQoL. Higher scores in the Healthcare Services scale indicate better experiences.

8.2.4.4 Mapping of Survivorship Issues to the LRRC-QoL and EORTC SURV100

The EORTC SURV100 was designed as a core module to assess HrQoL in cancer patients who remain disease-free 12-months following treatment, in place of the EORTC QLQ-C30 core measure (134). A mapping exercise was undertaken to compare the survivorship issues identified to the items in the LRRC-QoL and EORTC SURV100, to identify the level of coherence. This information could help in determining whether these measures can be used to assess HrQoL in long-term survivors of LRRC.

8.2.5 Reflective Log

A reflective log was maintained throughout the delivery of the study to critically evaluate the researcher's position and role within the research; identifying their own experiences and potential biases and how these may influence both the interviewing and analysis processes (320).

8.3 Results

Thirty-one patients were recruited to the study from ten sites across seven countries. Five patients were excluded following the interviews as they were found not to meet the eligibility criteria of remaining disease-free following treatment, resulting in data from 26 interviews with patients being included in the qualitative analysis.

8.3.1 Clinical and Demographic Characteristics

The clinical and demographic characteristics of the 26 patients included in the interviews are detailed in Table 8.1, 16 patients were male, and the majority of patients included were of white ethnicity. Median time interval since either diagnosis or surgical treatment for LRRC was 5.0 years (range 3.0-17.0). The majority of patients had undergone surgery for LRRC whereas 2 patients who had received neo-adjuvant chemo/radiation more than 3 years ago, had achieved a complete clinical response and remained disease-free following biopsy-proven LRRC. The range of surgical procedures described reflect the complexity and individualised nature of surgery in this disease setting. The purposive sampling strategy was adapted during recruitment due to the challenges experienced in meeting these criteria. This was particularly in relation to pre-operative treatment for LRRC; the criteria to include four patients who had been treated with pre-operative systemic chemotherapy was abandoned as this was not felt to have a significant impact on the results of the study and presented significant recruitment challenges.

Table 8.1: Demographic and clinical characteristics

Characteristics	**Participants (n=26) (%)**
Median Age (range)	70.5 (33.0-85.0)

Country	
United Kingdom	11 (42.3)
Sweden	7 (26.9)
New Zealand	1 (3.8)
Denmark	1 (3.8)
Canada	3 (11.5)
The Netherlands	1 (3.8)
Australia	2 (7.7)
Interview Setting	
Face to face	9 (34.6)
Telephone	16 (61.5)
Video call	1 (3.8)
Sex	
Male	16 (61.5)
Female	10 (38.5)
Ethnicity	
White	16 (61.5)
Black	1 (3.8)
Asian	1 (3.8)
Unknown	8 (30.8)
Marital Status	
Married	15 (57.7)
Living with partner	1 (3.8)
Divorced	1 (3.8)
Single	3 (11.5)
Unknown	6 (23.1)
Education Status	
Secondary school	5 (19.2)
College	8 (30.8)
University	3 (11.5)
Other	1 (3.8)
Unknown	9 (34.6)
Employment Status	
Self-employed	1 (3.8)
Full time employment	1 (3.8)
Part time employment	2 (7.7)
Retired	15 (57.7)
Other	1 (3.8)

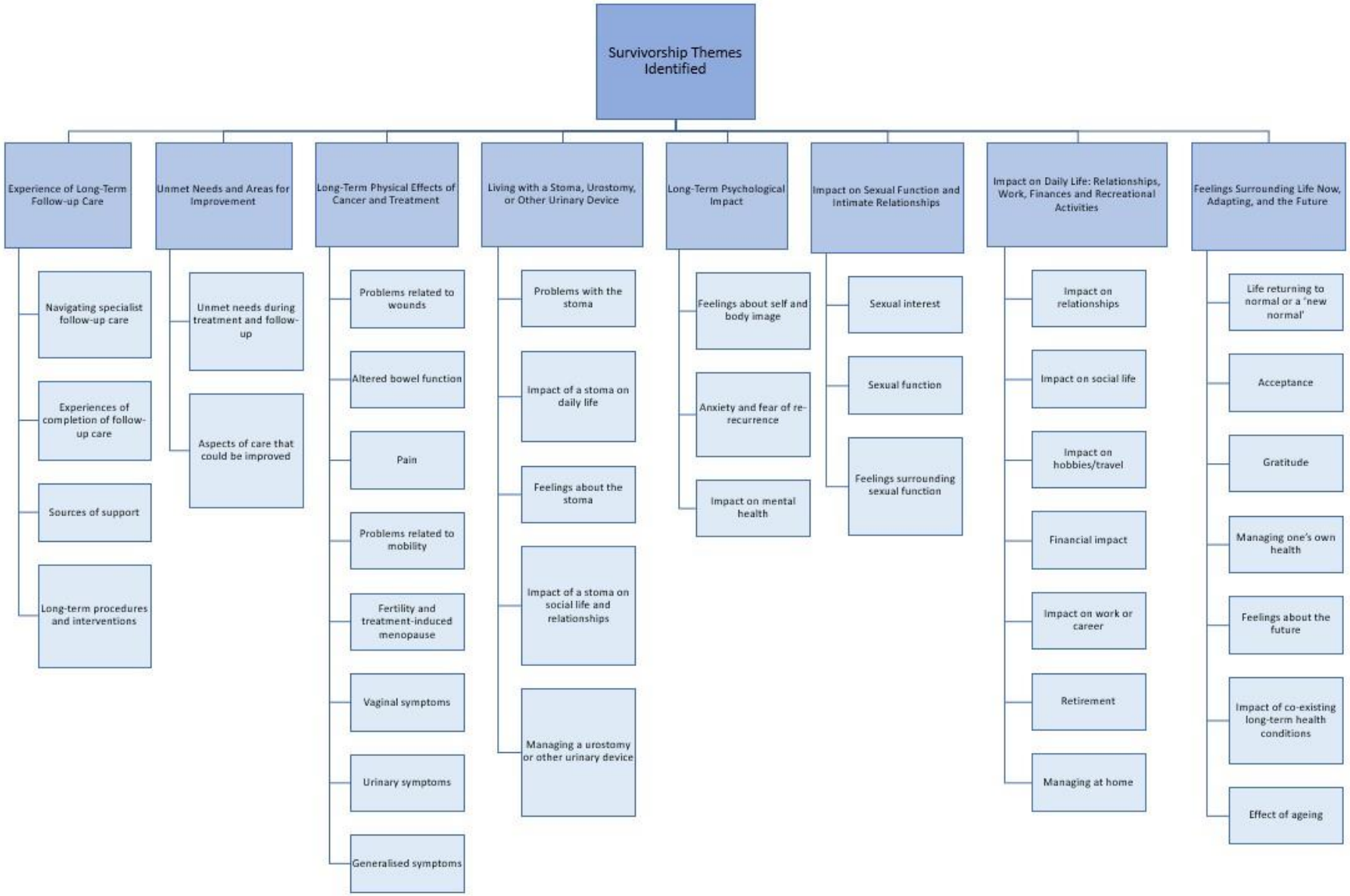
Unknown	6 (23.1)
Median Time Since LRRC in Years (range)	5.0 (3.0-17.0)
Mode of Detection	
Symptomatic	9 (34.6)
Surveillance	10 (38.4)
Unknown	7 (26.9)
Pattern of LRRC	
Anterior	6 (23.1)
Central	5 (19.2)
Lateral	8 (30.8)
Posterior	3 (11.5)
Unknown	4 (15.4)
Pre-operative Treatment	
None	10 (38.4)
Short Course Radiotherapy	2 (7.7)
Long Course Chemoradiotherapy	8 (30.8)
Long Course Chemoradiotherapy and Chemotherapy	1 (3.8)
Chemotherapy	2 (7.7)
Unknown	3 (11.5)
Operation Performed for LRRC	
Abdominoperineal excision	5 (19.2)
Abdominoperineal excision, hysterectomy, salpingo-oophrectomy and resection of vagina	1 (3.8)
Abdominoperineal excision, and resection and reconstruction of ureter	1 (3.8)
Abdominoperineal excision, S1/2 sacrectomy, ureteric catheters and Vertical Rectus Adbominis Myocutaneous (VRAM) flap	1 (3.8)
Cystectomy with Bricker and resection of small bowel	1 (3.8)
Extra-levator abdominoperineal excision (ELAPE)	1 (3.8)
ELAPE, right pelvic side wall resection and presacral fascia, reversal of ileostomy and formation of end colostomy	1 (3.8)
ELAPE, coccygectomy, prostatectomy, vesiculectomy, unilateral Inferior Gluteal Artery Perforator (IGAP) flap, distal ileal resection	1 (3.8)
Infralevator total pelvic exenteration, distal sacrectomy, reversal of loop ileostomy, end colostomy, ileal conduit and left IGAP flap	1 (3.8)
Low Hartmann's procedure	1 (3.8)
Pelvic exenteration: cystectomy, resection of ureter with Bricker, resection of vagina, neorectum left in situ	1 (3.8)
Posterior exenteration	1 (3.8)
Posterior exenteration, S3 sacrectomy, re-implantation of left ureter, excision of seminal vesicles and end colostomy	1 (3.8)

Rectal resection, ileocaecal resection and resection of ureter, end colostomy	1 (3.8)
Redo anterior resection and left Extended Lateral pelvic Sidewall Excision (ELSiE)	1 (3.8)
Right ELSiE and parastomal hernia repair	1 (3.8)
Total right pelvic sidewall excision with right salpingo-oophrectomy	1 (3.8)
None, complete response of biopsy confirmed LRRC to chemotherapy	1 (3.8)
None, complete response of biopsy confirmed LRRC to total neoadjuvant therapy	1 (3.8)
Margin Status	
R0	17 (65.4)
R1	3 (11.5)
R2	1 (3.8)
Not applicable	2 (7.7)
Unknown	3 (11.5)
Post-operative Treatment	
None	20 (76.9)
Chemotherapy	2 (7.7)
Unknown	4 (15.4)

8.3.2 Survivorship Issues and Themes Identified

Eight major survivorship themes were identified (Figure 8.2) and one theme related to Reflections on Adjusting to Life Following Diagnosis and During Treatment. The survivorship themes identified were: 1) Experience of Long-term Follow-up Care, 2) Unmet Needs and Areas for Improvement, 3) Long-Term Physical Effects of Cancer and Treatment, 4) Living with a Stoma, Urostomy or Other Urinary Device, 5) Long-Term Psychological Impact, 6) Impact on Sexual Function and Intimate Relationships, 7) Impact of Daily Life: Relationships, Work, Finances and Recreational Activities, and 8) Feelings Surrounding Life Now, Adapting and the Future.

Figure 8.2: Survivorship themes and sub-themes



Tables 8.2 and 8.3 contain a selection of quotations to illustrate the themes and subthemes identified in the analysis.

Table 8.2: Survivorship themes identified with illustrative quotations

Themes Identified	Quotations
Experiences of Long-Term Follow-up Care	
Navigating specialist follow-up care	"Even though it's a bit of a drive for me, I've found one that really gives personal care and attention, I feel that they know me, and they know my situation and that's very important." "The only thing I dread are these recurring trips to (the specialist hospital), using an expensive parking and finding my way in busy city traffic. That's a bit of a bother, but I'm happy to go there." "So, the thing that was really clear about all of the people that were involved and became my medical team, there was no holistic approach, it was all, everything was very siloed."
Experiences of completion of follow-up care	"Now if I had my way, if I had my way, this is probably slightly paranoid, I would still carry on having the scans, because as far as I'm concerned you can never be too careful." "Yes, yeah, but it's a bit of a. Yeah. It's sort of yeah, so it's a bit of a let-down, I suppose, a wee bit. You suddenly realise that you're on your own. Uhm…"
Sources of support	"My doctor is great, but I always feel rushed around them, with the waiting room full as it is. He's so busy, that I tell myself to hurry up, so you forget half of what you wanted to say/ask. With her however (specialist nurse), I'm at ease, taking my time. I can even email her with questions afterwards. I was really happy with this combined approach of physician and nurse" "I've got three daughters and one in particular was quite good in pushing me to get out of bed and pushing me you know, to become more active again."
Long-term procedures and interventions	"The doctor said they didn't want to do another one (sciatic nerve injection), they had quite a difficult time doing it because obviously my anatomy is strange. Everything is a bit lopsided!" "I had abdominal reconstruction, after the first surgery I had problems with hernias and they became very large and so I've had to have quite a few operations." "I would get these blockages where I would end up in emergency at the hospital, sometimes for 2-3 days and you know, would end up with an NG tube and all the other sort of stuff that went along with that."
Unmet Needs and Areas for Improvement	

Unmet needs during treatment and follow-up	"In terms of sort of like, you know, the physical aftereffects of surgery on my libido and things like that, that's just never been talked about actually really, and maybe that's remiss of me not to be more upfront and ask what they could do to help. But no, there's been very little aftercare." "To have some sort of counselling either one on one or group counselling, small group counselling, to work through some of these early-onset issues, because it's such a new thing and so different. Such a lifestyle change and just not something that you're ready for."
Aspects of care that could be improved	"I feel like, almost like painting by numbers, "this is what we do next, there's damage to the ureter and so we'll stent it, that's just what we do" and there was not actually any communication with me about what impact that would have on my life." "But no one said that! You know, but I was complaining about that for months, again before I had to say, can we test the hormones. Because they didn't put me on the hormones until I pushed to figure out what was wrong with me. They didn't say, "this is a result of the radiation", they were saying, "oh, I wonder why you're having hot flashes""
Long-Term Physical Effects of Cancer and Treatment	
Problems related to wounds, including abdominal wounds, perineal wound, rectal stump, and myocutaneous flaps	"I mean it discharges all the time, you know, if I don't wear underpants with pads on the inside, my bedcovers are covered in it in the morning, you know I'm forever washing them." "Err… well I found it difficult to wear a belt, I'd be given a belt to wear for support. The trouble was that the belt pressed on my buttock, where it was really painful and made it even worse, making my legs feel numb. So, I didn't get along very well with that."
Altered bowel function	"Things can move a lot quicker. Erm, but you know, when it first started, just after the surgery, well it was more after the radiotherapy I suppose, I thought that I'd never be able to go on a long day hike or go camping or things like that, things that I really love. So, that's improved so much really and I am pretty free. I don't feel that it really stops me, I mean, if my movements are a lot quicker than I want them to be, I can just take some immodium, that's pretty manageable."
Pain	"Erm, the… because of where the radiation was, I feel that there's a lot of nerve, well I know there's a lot of nerve damage. So sometimes I'll just have like a sharp shooting pain, they tend to go away if I kind of adjust the way I'm sitting or move my legs or whatever. But yeah, that will be like right inside cervically." "I've got pain from my buttock going down my right le down to my foot. It's like a burning pain, as if I've got some nerve damage from the operation."
Problems related to mobility	"Socks and shoes, you sort of can't really bend down so much and put them on so easily, for some reason. But I just sort of tend to kneel down on the floor and do it. So yeah, I mean it's just one of things." "Well, I'm disabled now." "In terms of the nerve endings, my hands and feet are really sensitive now. The soles of my feet, I have problems… they're just really sensitive."

Fertility and treatment-induced menopause	"I mean we're so blessed to have our one gorgeous child, so you know, not having to worry about freezing eggs or any of that, we were just really happy that we have one child, who we adore. That was a nice thing to go through and think actually I don't need to worry about all of the extras surrounding fertility and cancer care. Yeah, so that was actually an easy decision to make really, not having to think about what do we want to do for our family." "Oh, just the feeling of, like the, just like crying all the time and not being able to put my finger on the reason. Even though I was struggling so much with my health, you know, I wasn't pointing to that, that couldn't just be the only reason that I was so emotional."
Vaginal symptoms	"Initially, I was very worried about that. 'How's that possible, I can't be menstruating (after the surgery), so what can it be?' I've had frequent checks with the gynaecologist, including a pelvic exam, and I had oxygen therapy, but nothing has changed. It's still the same, even now. My gynaecologist has tested and examined me for it since 2019. Nothing has changed though, it keeps coming, so I just accepted it."
Urinary symptoms	"With a Tena nappy. I make sure I've got one in the car and one with me, wherever I am. Erm and make sure I'm wearing a skirt, or a dress, so that I can quickly tear the sides and put it on. So that I can actually go, because several times I've been caught out." "Yes, there was a slight change; I don't feel the last bit. When there's pressure on my bladder, I can urinate as before. Not that last bit though: Oops, there's still more!"
Generalised symptoms	"Generally, I suppose, since the operation I think I've probably felt more tired, you know towards the end of the day." "But I can't drink hot coffee, or tea, not too hot, it has to cool down a bit, because I get blisters in my mouth… But I think if it's not worse than what I have then I'll put up with it"
Living with a Stoma, Urostomy, or Other Urinary Device	
Problems with the stoma	"It bleeds sometimes around the edges." "The stoma size has changed over the years and so I have had to go see stoma nurses to help re-fit things if I was experiencing leakages, erm... or leakage or just like, different kinds of friction or whatever."
Impact of a stoma on daily life	"I try not to be too far away from a toilet because it's something that you have to manage quite regularly and unfortunately it does dominate… it can dominate a large part of the day." "Then I went to the local hospital and the two nurses there told me about irrigation and as far as I'm concerned, irrigation has completely changed my life."
Feelings about the stoma	"But yeah, I couldn't even look at it to start with, I couldn't bear to look at it, never mind touch it or clean it or change it, you know." "I just take it as a part of life, it's a necessary evil that has to be performed." "Yeah… but it took me, uhm, I suppose. But even now, it's sort of, you know… It took me 5 years before I would go swimming. Uhm? And that was just self-conscious. Just me being aware I had a bag sticking on me, on the front…"

	"I'm really happy with my colostomy… my quality of life is a lot better with that than with the TME procedure. If I had to make a long trip for my work, I left the house with diapers on."
Impact of a stoma on social life and relationships	"Well, I think probably just, I'm always thinking about "is my bag showing?" I don't mean hanging out of my clothes, just the actual shape, does it show. If I'm in a close social event, with people close by, then I think about the farting part of it. So, I'm sort of conscious."
Managing a urostomy or other urinary devices	"Erm, during the day for some reason I can, but at night if I go to sleep then I leak from my penis sort of thing." "It's an urgent need to go to the loo but the end result, I'm not going anywhere with it because I can't use it" (patient with urostomy) "I don't wear a leg bag anymore but I used to wear it… I clicked the valve once when I was talking to people and once the valve came off when I was going round the supermarket." "Painful. Yeah… painful having them (nephrostomies) changed."
Long-Term Psychological Impact	
Feelings about self and body image	"My stomach, my lower stomach and my backside look a mess but there aren't too many people I show them to." "Erm, well, I haven't had a physical relationship with anyone for years now but I wouldn't have felt confident to anyway", "You know, the sight of the hernia and all the bits and pieces that are missing now (laughs), I wouldn't have been very body-confident."
Anxiety and fear of re-recurrence	"Before I would just go out and do something, I can build this and I can do that and it was quite easy, but after the operation I had a lot more anxiety about doing things and I ended up on pills for a wee while, but I'm not on those anymore." "Just definitely… I mean, I had a little flash of it when you phoned me, whenever I see that unknown caller sign come up on my mobile phone." "I'm 3 years in remission now but last time I went after 5 years I found out I had recurrence so that's the one thing that is lying dormant at the back of my mind and hoping that that doesn't happen again."
Negative effects on mental health	"Well it makes me a bit miserable at times. I was always a very active person. I can walk, I can walk around town like yesterday but when I get home, I sort of end up wishing I hadn't, I'm in that much pain with it." "I think most people go through a little, well I suppose grieving for your former self."
Positive effects on mental health	"Just having gone through it twice, you know, it gives you a totally different outlook on life and it makes you realise how precious life is" "yeah, I mean, erm, I'm a Christian, so I believe everything that the Bible says to be true and one of the things for me is that it has increased my faith. I had a very strong faith before but I believe my faith is even stronger now."
Impact on Sexual Function and Intimate Relationships	
Sexual interest	"So, I definitely… it's difficult to unpack which is HRT and menopause related but definitely my drive has much decreased." "we still do it, but with a lot less penetration. It's not always nice. Nor do I know why I'll 'allow' it sometimes, and not at other times. So we can

	do it, and it 'works', but because of this painful moment, I sometimes decline."
Sexual function	"I did, through surgery, sustain a little bit of nerve damage to my vulva and around my clitoris which was slightly disappointing in that regard, so I don't have as much sensation down there as I used to." "certainly, sexually, everything has changed because, with the treatment, not the surgery but the radiation, completely shrunk my vagina and my cervix and so I can't have intercourse in the same way." "yes, there's no sex now. There's nothing happening down there at all (erectile dysfunction)."
Feelings surrounding sexual function	"erm, I manage fine. When you get to my age, it doesn't make a lot of difference quite frankly (laughter). You can't make an omelette without breaking eggs and we just carry on, I still enjoy life, so it's fine." "But now, it's just no luck. And I do pity myself, it's the one thing that I do pity myself, because I did enjoy it" "Penetration used to be always part of our sexual relationship, but not anymore. It's not a problem for me though, nor for my husband." "My self-image has changed a lot though: I hate the sight of my vagina with that flap that was folded inwards to close my anus and repair the backwall. So there are indeed positions that are a no-go for me; I really don't want him to see me like that."
Impact on Daily Life: Relationships, Work, Finances and Recreational Activities	
Positive impact on relationships	"Yeah, I think the whole family has come closer together, even our children are closer to one another, you know, not just closer to myself and my wife." "One really positive thing to come out of it is to be much more upfront and open", "So it has allowed me, it's given me the balls and the confidence to be like "I'm not handling things very well today, I really need a bit of space" or "I need a bit more help with this" so that's really positive I think."
Negative impact on relationships	"Well, I don't see my friends anymore, there's only one I'm in touch with. He comes up to visit... I've lost touch with other friends." "I mean it's very, very difficult, knowing the stress I've put on my nearest and dearest. Not through any fault of my own but I know it was hugely traumatic for a lot of people I really, really love and that was quite difficult."
Impact on social life	"I don't want pity. I want somebody just to talk to, who won't feel sorry for me." "In the social area, there's nothing that I did before that I couldn't do afterwards if I chose to."
Impact on hobbies	"I simply can't anymore. It's no good, I have handed in our golf equipment, which is the saddest part about it, I can say. Consequently, I cannot walk that far." "The things that I enjoy doing, I enjoy doing things around the house, DIY and working on the cars. I enjoy making things and you know, I'm still able to do those things which I enjoy."
Impact on holidays/travel	"It's always difficult for me now getting insured to go, getting insured to go somewhere like New York would just be an impossibility. Er, just in

	case, the worst came to the worst, and I needed to be admitted into hospital anywhere. I couldn't get covered for existing illnesses." "I'm always wary of going anywhere in case I get an infection while I'm away, you know."
Financial impact	"I pay about between $600-650 per month for my pouches and gadgets that I need for my colostomy." "but obviously my wife had to sort of keep work going really to keep income coming in", "she lost her job over it (stress) in the end, she ended up changing jobs."
Impact on work or career	"I had no choice, I had to stop work. I had no choice." "well, to be honest, it probably helped because it gave me something to focus on rather than the illness itself at the time."
Retirement	"I felt very disappointed at first because you know, retiring, I'd worked so hard. I worked as a nurse for 43 years and you know, you feel a bit angry and disappointed that as soon as you retire, everybody dreams of being able to travel and do all sorts of things and I just ended up as a patient." "erm, well I enjoy retirement, there's not enough hours in the… sorry, not enough days in the week to get it all done really (laughter), no I don't have any issues with that. Nice garden, grandchildren have arrived, all the trappings of someone in their seventies really."
Managing at home	"If I wanted to go shopping, I couldn't go shopping on my own. Wherever I needed to go, I just couldn't go on my own." "because I can't stand for very long to do any washing up or any cooking. So, I've got carers to come and do the cooking and the cleaning."
Feelings Surrounding Life Now, Adapting and the Future	
Life returning to normal or a 'new normal'	"apart from the impotence, I've gone back to normal life, you know" "well, I've tried to conduct my life as normal as possible because I fear that I nearly lost it during the second operation and obviously I was in hospital for about 9-10 months which was really unpleasant for me and my family."
Acceptance	"It's the mental side of it, you have to basically try and tell yourself that "you're here" and that's how you have to conduct your life, then it's better than not being here and losing your life." "There's nothing about my… everything else has been a challenge, you know, what I've had to work through at work, it just affects everything, everything else, so the only way that it can be positive is through acceptance."
Gratitude	"I'm in a very good position at the minute, I'm a lucky bloke, like I say, I've got a lot of life to live, I'm self-sufficient. I've got a nice new little bungalow, my partner's got her own place, so we go on nice holidays and do things." "But I owe everything to the National Health Service and the people who work for it."
Managing one's own health	"So yeah, anyway, I had chemo when I was on the opioids and I became very sick. So, I had a friend who suggested I should try cannabis, which I did, and I found that the cannabis made me… it took away the pain, not

	for as long as the opioids did but it did take away the pain very effectively. It did help with nausea, and it made me eat better, I could eat again." "I couldn't handle it, it wasn't it for me, I felt that I needed to go out and be as active as possible."
Positive feelings about the future	"Erm but you know, I've done it a couple of times, I can always do it again. And who's to say that people won't have knocked cancer on the head by the time I ever grow anything new, so the future feels good and positive." "There are a couple of things in my life that are very important to me. Like my son, I have a great relationship with my son. I'm now more of the 'making memories' type than before. If I haven't heard from him for a while, I feel it's a pity: 'Suppose that by next year, I'm gone, than we really missed out on some time together.'"
Negative feelings about the future	"I do know, in the future, I will start to have problems. You know, as you get older, I've still got to do all this bag changing and everything else but I do know that's going to happen." "You've got an uncertain future, haven't you? You can never plan too far ahead because you don't know what the future holds."
The impact of co-existing long-term health conditions	"I know in recent years, I haven't really been on holidays abroad or anything, you see, my major problem with me is my COPD. That's gotten worse and worse, of course that does affect you because your breathing becomes very difficult. You know, where I didn't know or suffer any real pain with the cancer but I'm suffering with the COPD."
Effect of ageing	"Of course, it's not like it was before the surgery, but I'm having trouble determining whether it's due to the cancer or my age. I don't know it as well as I used to, but I've also gotten older."

Table 8.3: Feelings on Adjusting to Life Following Diagnosis and During Treatment theme with illustrative quotations

Reflections on Adjusting to Life Following Diagnosis and During Treatment	
Positive feelings surrounding diagnosis and treatment	"I actually wasn't bothered at all; all I wanted was to stay alive. What I thought was: rid yourself of every suspicious element." "The second time round, I think, you have a little more confidence just to sort of, trust your body and to identify what the feelings are and so yeah, I don't feel like I needed as much care the second time round", "Even though, the surgery was far more complicated and had a lot more sort of, aftereffects, symptoms. I suppose like childbirth, the second time round is just a bit less terrifying."
Negative feelings surrounding diagnosis and treatment	"it's a very frightening and scary process". "I had this brand-new relationship, so I worried if intercourse would still be possible, that sort of thing. Not so much for me, I just wanted it gone. I did worry about my relationship though, whether it would last."
Decisional regret and other feelings surrounding the decision to have	"like if I had to choose between knowing this would happen to me with radiation and risking having to have a permanent colostomy, I would have chose permanent ostomy without ever doing the radiation."

surgery and other treatments	"Later on, I fiercely regretted removal of my uterus and ovaries; the 'change' was very hefty. The menopausal symptoms were a huge burden."

8.3.2.1 Experiences of Long-Term Follow-up Care

This theme explores the experiences and feelings surrounding long-term follow-up care and issues which relate to long-term follow-up care.

8.3.2.1.1 Navigating specialist follow-up care

All patients interviewed received their surgical care for LRRC at a specialist tertiary centre, often geographically distant from where they lived, with an impact on their experiences of long-term follow-up care and surveillance. Some patients expressed their willingness to travel for follow-up at a specialist centre. Whereas others reported the impact on their time and finances of attending follow-up appointments further from home, including travelling long distances and paying for parking. Ultimately, some patients had opted for their follow-up to be transferred back to their local hospital due to the travel required.

The co-ordination of care between specialist and local teams and between different specialties was also identified as a challenge, with patients highlighting that communication between these could be disjointed. Patients were also frustrated by the need for repeated scans due to the poor quality of scans performed at local hospitals. One of the patients also reported finding it difficult to know which team to contact due to management being shared between different teams.

8.3.2.1.2 Experiences of completion of follow-up care

Several of the patients interviewed had come to the end of their follow-up care, typically after a minimum of 5-years (43), and discussed their experiences and feelings surrounding this. Feelings were mixed, some patients felt relieved and were positive about being discharged from follow-up, patients were particularly reassured that they were able to contact the specialist team if needed. Other patients would prefer to continue having follow-up, particularly scans to monitor for signs of recurrence. One of the patients found the transition difficult and felt alone now that their follow-up was complete. Another patient reported missing their clinical team. One of the challenges that patients reported was transitioning back to care supported solely by the GP given their lack of specialist knowledge regarding LRRC.

8.3.2.1.3 Sources of support

Participants reported various sources of support during their follow-up care, this included support from healthcare professionals, including consultants, specialist nurses, nursing staff and General Practitioners. Some patients even highlighted the care they had received as the main positive aspect of their overall experience. Support specifically from specialist nurses was highlighted by several patients, with one of the patients stating that the specialist nurses having more time was important to them. The importance of the patient being involved in decisions and experiencing personalised care from their stoma nursing team was highlighted. Good bedside manner was also identified as something which helped patients feel supported by their clinical team.

Other sources of support included friends, family, and partners. Patients also identified their family as a motivating factor in their recovery, particularly spending time with their

grandchildren. Several of the patients reported experiencing support from their work and/or employer, one patient was able to access additional support and resources through their employer. Other sources of support were cancer charities and organisations, support groups, and support from others with similar experiences, however not all patients found these kinds of resources helpful.

8.3.2.1.4 Long-term procedures and interventions

Many patients had required interventions or additional procedures for complications following their treatment for LRRC. These issues included steroid injections to the sciatic nerve for pain, skin grafts for wound problems, re-operations, and examinations under anaesthetic for a perineal sinus, a referral to neurology for foot drop, admissions to hospital with small bowel obstruction and in some cases a laparotomy for small bowel obstruction. One patient underwent abdominal reconstruction due to incisional hernias and three patients required a parastomal hernia repair.

8.3.2.2 Unmet Needs and Areas for Improvement

Several unmet needs were identified relating to treatment and follow-up, in addition to aspects of care that could be improved.

8.3.2.2.1 Unmet needs during treatment and follow-up

Patients identified several needs which they felt had not been met during their treatment or follow-up, these included information regarding nutrition and diet, one of the patients also reported experiencing a lack of adequate advice regarding their diet in relation to managing a temporary ileostomy. One patient felt that counselling specifically in relation to having a stoma would be helpful both before and following their operation.

Two female patients reported a lack of discussion regarding their sexual function during their follow-up care, they particularly felt the emotional and psychological impact of impaired sexual function was not addressed. Male patients also reported a lack of discussion of their sexual function during follow-up, though this included not wishing to pursue further treatment options such as penile injection therapy. One of the female patients also felt that the information she received regarding the potential effects of treatment on sexual function, particularly vaginal atrophy, was inadequate. They also identified the lack of effective treatments for vaginal atrophy as an unmet need.

8.3.2.2.2 Aspects of care that could be improved

Communication was identified as an aspect of care that could be improved, this included communication between clinicians and patients regarding their care, extending to involving patients more in decisions regarding their care. One of the patients also highlighted the provision of emotional support from their clinical team as something that could be improved, feeling that their care lacked a holistic approach. Another patient felt that the communication with their clinical team was lacking in compassion following experiencing a complication, feeling that their team was scared that they would make a complaint. As described in the sub-theme, Navigating Specialist Follow-up Care, communication between different hospitals and clinical teams was highlighted as something that could be improved during the delivery of follow-up care, in addition to access to better quality MRI scanning at peripheral hospitals.

One of the other aspects of care that patients felt could be improved was more frequent contact with their clinical team and a greater level of support, particularly in the

community and from the stoma nursing team. Earlier recognition and diagnosis of treatment-induced menopause was another aspect of care that was highlighted as something that could be improved.

8.3.2.3 Long-Term Physical Effects of Cancer and Treatment

The majority of patients participating in the study experienced some form of long-term physical effect as a result of their cancer and/or treatment which have been further grouped to reflect similar symptoms or issues.

8.3.2.3.1 Problems related to wounds, including abdominal wounds, perineal wound, rectal stump, and myocutaneous flaps

Some patients described experiencing long-standing symptoms related to their perineal or buttock wounds, including symptoms related to a perineal hernia, such as pain or discomfort. Other patients described issues related to perineal sinuses or fistulae which continued to have a significant impact on their lives, particularly the experience of recurrent painful infections. One of the patients described experiencing ongoing discharge from a perineal sinus which affects their daily life, including impacting on their sleep due to ongoing discharge. Whereas another patient experienced frequent pruritis. One patient ultimately required re-intervention which had resolved their symptoms whereas others continued to experience symptoms years after their operation.

In relation to abdominal wounds, three patients described experiencing issues related to a parastomal hernia, all had undergone further surgical repair. One patient was particularly worried about the physical appearance of their parastomal hernia and that it would be visible through their clothing, particularly in social situations. Another patient

described the long healing process for their myocutaneous flap and how this had limited their ability to exercise.

8.3.2.3.2 Altered bowel function

Two patients interviewed had not required formation of a permanent stoma at the time of their operation for LRRC. Both experienced altered bowel function, including features of LARS such as loose stool, urgency, and frequency, during and following their treatment for LRRC. This prevented them from doing things they enjoyed such as going camping, however the symptoms had improved over time.

8.3.2.3.3 Pain

Many of the patients interviewed continued to experience chronic pain, some patients described experiencing pain in their buttocks or perineum, particularly on sitting. Other patients experienced ongoing lower limb pain, including chronic pain related to the sciatic nerve, or pain in their groin or abdomen. Patients also described the impact of experiencing chronic pain on their daily life including sleep, and avoiding specific activities, such as cycling, due to pain. One patient described experiencing pain in their rectum, particularly in relation to opening their bowels.

8.3.2.3.4 Problems related to mobility

Participants described the issues they experienced with their mobility and the adaptations they had made to help them to cope and manage this. Issues included leg weakness and swelling, pain and stiffness. These all had an impact on function, for instance the ability to put on one’s socks and shoes. Adaptations that patients had made included needing to take more caution when mobilising due to leg weakness. Other patients also reported a

reduction in their mobility and requiring mobility aids, particularly for longer distances. One of the participants described undergoing rehabilitation and finding his helpful in regaining strength. Foot drop, a long-term effect of sciatic nerve resection, had an impact on patients' mobility and physical function, causing them to be less active. Patients particularly found stairs challenging and many of the patients experiencing foot drop described needing to use walking aids. One of the patients identified themself as "*disabled*" due to their foot drop.

Some patients had received chemotherapy during their treatment and experienced long-lasting peripheral neuropathy as a result, causing their hands and feet to be more sensitive, particularly to cold weather. This affected their ability with fine motor tasks and physical work related to their job.

8.3.2.3.5 Fertility and treatment-induced menopause

Two female patients participating in the study were diagnosed with LRRC prior to experiencing the menopause which impacted on their experiences and treatment decisions. One patient was diagnosed with LRRC in their thirties and identified the need to consider options surrounding fertility prior to commencing their treatment, ultimately, they decided that their family was complete and did not pursue this.

Both patients described issues related to the intense and rapid onset of treatment-induced menopause, including symptoms such as hot flushes and a significant impact on their cognitive function and mental health, experiencing low mood. Both patients had accessed hormone-replacement therapy (HRT) and found this positive. One of the patients felt that communication and accessing treatment for the menopause was an aspect of their care

that could be improved, as previously highlighted. Overall, these issues are unlikely to affect a significant proportion of patients with LRRC yet have a significant impact on those experiencing them.

8.3.2.3.6 Vaginal symptoms

One of the patients interviewed described experiencing ongoing vaginal bleeding which had caused them anxiety and required further investigation, they had now accepted their symptoms could not be resolved and managed them by placing gauze in their underwear.

8.3.2.3.7 Urinary symptoms

Several patients experienced ongoing urinary symptoms which affected their daily life. Patients experiencing urinary incontinence described needing to carry additional clothing with them and/or needing to change more frequently, they also described using adult nappies to manage their symptoms. One patient was awaiting a sacral nerve implant to help manage their symptoms. Other patients experienced difficulty voiding urine, one patient had received medical treatment for this, another patient experienced reduced sensation on voiding their bladder, particularly at the end of micturition.

8.3.2.3.8 Generalised symptoms

Some patients had experienced generalised symptoms including fatigue which had continued to affect them in the longer term. One of the patients also reported their sleep pattern being worse since they had undergone treatment for LRRC. Another patient had experienced oral mucosal problems following chemotherapy, meaning they were unable to drink hot drinks.

8.3.2.4 Living with a Stoma, Urostomy or Other Urinary Device

Several patients were now living with a stoma, urostomy, or other urinary device as a result of their treatment for LRRC, which continued to affect them in different ways.

8.3.2.4.1 Problems with the stoma

A range of issues with stomas were reported including bleeding from the stoma, leaks from the stoma bag, skin excoriation due to the stoma output, and high stoma output. One patient reported difficulty managing their stoma in hot weather as sweat would affect the seal, achieving a seal around the stoma bag could also be affected by changes in the size of the stoma or parastomal hernias.

8.3.2.4.2 Impact of a stoma on daily life

Several patients reported the ways in which having a stoma impacted their daily life, these included the stoma affecting their sleep, particularly if the bag leaked. The necessity for access or proximity to toilet facilities was also described, which impacted on the way in which patients would plan their day. One patient also described specific difficulties associated with changing their stoma when out of the house, such as kneeling down to empty the stoma bag contents into the toilet, which can be unpleasant if facilities are not clean. Another patient described always carrying stoma supplies with them to prevent being caught out by bag leaks.

The impact of diet on stoma function was also reported, with patients having to adapt their diet following stoma formation. One patient reported managing their stool consistency using medication to prevent stoma bag leaks, another patient used irrigation to manage their stoma and had found this transformational in helping them to control their

output. One patient described the way in which their stoma affected them at work and how it had changed their behaviour to try and mask their stoma, in addition to always sitting near to an exit in case of stoma bag leaks. One patient reported the stoma affecting their sleep due to needing to wake to empty gas produced by flatulence from the bag.

8.3.2.4.3 Feelings about the stoma

A range of feelings were identified in relation to living with a stoma. One of the patients interviewed reported feeling relieved that they had not required a stoma following their surgery for LRRC. Other patients described the difficulty they had experienced in accepting their stoma, particularly following their operation, describing not being able to "*bear to look at it*" initially. Other negative feelings regarding stomas included embarrassment, particularly in relation to bag leaks. Body image was also identified as having been impacted negatively by having a stoma, with patients describing feeling self-conscious. Patients also reported the psychological impact of adapting to life with a stoma and that this could be depressing when experiencing difficulties.

Several patients reported learning to manage their stoma and feeling more positive about it over time, with one of the patients reporting that this learning process was ongoing. Some patients felt positive about their stoma, particularly those who had experienced poor pre-operative bowel function.

One patient described their stoma as a disability, others reported that their stoma was, "***the*** *biggest physical change*", but they had "*just tried to conduct my life as normal as is possible with a stoma*".

8.3.2.4.4 Impact of a stoma on social life and relationships

Various ways in which a stoma could impact on social life and relationships were described, this included avoiding social activities which are far from toilet facilities and extended to avoiding travelling to places where facilities may not be as good. One patient described being apprehensive, particularly in new social situations due to concern that their stoma might be visible.

8.3.2.4.5 Managing a urostomy or other urinary devices

Two patients reported having a suprapubic catheter in situ, one found that this could be challenging to manage, and the other patient continued to experience leakage from the bladder despite this. A significant challenge identified was managing leaks from the bag. One patient described experiencing occasional urgency to pass urine despite having a urostomy, describing it as "*torture*". Other patients had experienced ureteric stents or nephrostomies, finding it difficult to change the bags themselves as they were unable to reach them, "*yeah it's the only thing I can't do myself*". They also described the process of having them changed as painful. One of the patients described their experiences of regular ureteric stent changes more positively, whereas another patient had experienced complications related to a stent removal, resulting in a urinary tract infection. One patient had experienced recurrent urinary tract infections in relation to their urostomy, requiring admissions to hospital. Other patients reported positive experiences and feelings related to living with a urostomy, including not needing to wake at night to urinate.

8.3.2.5 Long-Term Psychological Impact

Several issues relating to the long-term psychological impact of experiencing LRRC and its treatment were identified.

8.3.2.5.1 Feelings about self and body image

Several patients described their feelings in relation to their body and physical appearance and how they have been affected by their experience of LRRC. This included feeling conscious of scars to their abdomen and perineum. Patients also described how their feelings about their body affected their confidence, particularly in the context of a romantic relationship. Two patients who were not in relationships felt they would not be confident to be intimate with a new person due to their feelings about their body.

8.3.2.5.2 Anxiety and fear of re-recurrence

Patients described experiencing anxiety in a range of circumstances related to both their disease and treatment, including experiencing generalised anxiety and reduced confidence. Anxiety in relation to scans and waiting for scan results was also described, particularly fear of re-recurrence. One of the participants described the way in which their specialist team had helped them to navigate scan-related anxiety by calling them in advance of sending out letters detailing scan results or upcoming scans. Anxiety related to unanticipated phone calls or calls from a withheld number was also identified as something that had stemmed from experiencing cancer.

Fear of re-recurrence was a key source of anxiety for several patients, one participant described the pervasive impact of these thoughts and how they thought about it all the time as they had recently experienced pain and associated this with cancer.

8.3.2.5.3 Impact on mental health

The experience of LRRC and its treatment had had a lasting negative impact on the mental health of some participants. Long-term symptoms particularly impacted on patients' mental health, this included experiencing chronic pain and functional limitations, affecting their mood. Chronic wound problems also had an impact on mental health and the prospect of requiring further procedures for complications affected patients negatively from a psychological perspective.

Patients described experiencing low mood, with some having been treated with antidepressant therapy. Feeling a lack of control was another way in which patients described their experiences, particularly during the period when they were recovering from surgery. Some patients had felt isolated as a result of their disease and treatment, having lost contact with their friends and previous social life. One of the patients felt that having a stoma had been particularly isolating. Feelings surrounding trying to return to a 'normal' life or to their previous way of life prior to their illness were complex and difficult to navigate, finding it difficult to adapt to life following cancer. One patient described experiencing grief for their life and the person they had been prior to cancer.

Not all of the impact on mental health was negative, with patients identifying positive effects of their experience and things which had helped them to cope, these included resilience, having a positive attitude and developing a renewed appreciation for life. Several patients described their strong mental resilience as something which had helped them through their experience and in their life following treatment. The importance of positivity was also described, particularly in relation to recovery. Some of the patients described developing a greater appreciation for life following their experience of LRRC,

patients also described finding reason in their lives or strengthening of their existing faith, this extended to helping others through voluntary work and finding this rewarding.

8.3.2.6 Impact on Sexual Function and Intimate Relationships

The way in which LRRC and its treatment had affected sexual function and intimate relationships was identified as an issue which continued to impact on patients.

8.3.2.6.1 Sexual interest

Reduced interest in sex was described, particularly in relation to having experienced treatment-induced menopause. Sexual interest was also described as having been impacted by alterations in sexual function; one of the patients experienced pain during penetrative sex following their treatment which had negatively affected their interest in sexual intercourse.

8.3.2.6.2 Sexual function

Both male and female sexual function were affected by LRRC and its treatment, some male patients described experiencing erectile dysfunction to the extent that they were no longer able to have sexual intercourse, "*yes, my sexual life is non-existent*". Another patient reported successfully using medication to help with erectile dysfunction. One patient was not able to access this due to their cardiac history. Female patients described experiencing discomfort during sexual intercourse following their treatment for LRRC. Impaired sensation was also described due to nerve damage affecting the vulva and clitoris. One patient was unable to partake in penetrative intercourse due to vaginal atrophy.

8.3.2.6.3 Feelings surrounding sexual function

Feelings surrounding the impact on sexual function were mixed, some patients had accepted their new level or lack of function, feeling that this did not impact significantly on their life, others had adapted their sex life to be intimate without penetrative intercourse. One of the patients felt very positive about their sex life, despite a lack of spontaneity associated with using medication for erectile dysfunction, "*it's really great, the only problem is, you've got to plan ahead to do that! But no, I would say, other than that, I mean our sex life is great, no problems at all*."

Other patients had found it much more difficult, describing feelings of self-pity, one female patient describing their inability to have penetrative sex as, "*that is probably, I would say the hardest thing to deal with both emotionally and physically*". They had also found using vaginal dilators difficult emotionally due to associating them with sexual trauma. Negative body image could also affect confidence during sexual intercourse, one patient described avoiding certain positions during sexual intercourse as they did not want their partner to see parts of their body which had been affected by their surgery.

8.3.2.7 Impact on Daily Life: Relationships, Work, Finances and Recreational Activities

The experience of surviving LRRC had impacted on patients' daily lives in a number of ways, including relationships, work, recreational activities, and their finances.

8.3.2.7.1 Impact on relationships

Ways in which relationships had been strengthened and impacted on positively were described, including patients' families becoming closer following LRRC. The importance

of having a supportive family and/or partner was also identified, in addition to learning to accept more help from one's family. One patient described a change in their approach to their close relationships following their experience of LRRC, finding that they were now more open in communicating their needs or difficulties they were experiencing.

Patients also reported ways in which their relationships had been negatively affected, some had lost touch with friends following experiencing LRRC. Another patient described the difficulty in maintaining some relationships in relation to negative attitudes towards cancer within their culture. Some patients had experienced a breakdown in their relationship with their partner, causing them to divorce, or had experienced conflict in their close relationships due to their experiences, particularly when they were experiencing unpleasant symptoms such as pain. Others had felt they had put their friends and family under stress and found that difficult. One of the patients highlighted the impact of LRRC not just on them but on their family too, describing how their partner had needed to maintain their job to support them financially in addition to experiencing the psychological impact of their partner being unwell.

8.3.2.7.2 Impact on social life

Patients' social lives had been impacted by LRRC, finding it challenging to return to socialising with friends due to concerns that they would be treated differently, and not wanting to be pitied. This was particularly identified as being the case when meeting new people and feeling concerned they would not understand their experience or that they had a stoma. Others described positive experiences and had managed to maintain a good social life throughout.

8.3.2.7.3 Impact on hobbies/travel

Recreational activities and hobbies were highlighted as an aspect of life that had been significantly impacted by LRRC for many patients, particularly physical activities which they were no longer able to do, such as golf, table tennis, and cycling. Other patients described being able to continue with their hobbies, particularly those which were less physically demanding, such as playing bowls, walking, DIY, gardening, swimming, and some were still able to play golf.

For many patients, travel was still possible but very different following their experience of LRRC, particularly the need to bring medical supplies and equipment to manage stomas or other physical effects of treatment. Some patients identified concerns regarding managing their stoma as a barrier to travelling. Travel insurance was also identified as a significant barrier due to being too expensive for patients who had been treated for cancer, in addition to fears of becoming unwell whilst away from home.

8.3.2.7.4 Financial impact

There were several financial implications associated with experiencing LRRC, for some patients, this included paying for their stoma supplies which had a significant impact on their finances. Some patients had been able to access Personal Independence Payments (PIP) whilst they were unwell which had helped support them financially however these had now stopped, insurance was another way in which patients had received financial support whilst receiving treatment. The financial implications also extended to partners and family, who had felt pressure to continue working to support the family.

8.3.2.7.5 Impact on work or career

Many of the patients interviewed had been working at the time of receiving their diagnosis with LRRC and in the long-term this had had an impact on their work life. Some patients were unable to return to work at all following treatment and others experienced the challenges associated with returning to work, with a variety of associated feelings. For some patients, returning to work was not an option, others described being limited in the work they were able to do following LRRC.

Some patients who were able to return to work described enjoying this, two patients even described continuing to work from their hospital bed and finding this a helpful distraction. Others felt that returning to work following treatment helped to keep them active. Flexibility in working practices was helpful for those who had returned to work.

8.3.2.7.6 Retirement

Many patients were now retired, for some this was the case prior to diagnosis with LRRC and for others they retired following this. Patients described the ways in which their retirement had been affected, with some having been forced to retire when they became ill. Another patient had recently retired at the time of their diagnosis and felt angry that their illness had impacted on their plans for retirement, whereas other patients were enjoying their retirement and life following LRRC. One of the patients described using their retirement to volunteer and help others and found this rewarding.

8.3.2.7.7 Managing at home

For some patients, the ability to manage at home with their activities of daily living had been negatively impacted long-term following their experience LRRC, requiring support from carers in their daily lives.

8.3.2.8 Feelings Surrounding Life Now, Adapting, and the Future

Several feelings surrounding life now, how patients had adapted following their experience of LRRC and how they felt about the future were described.

8.3.2.8.1 Life returning to normal or a 'new normal'

The concept of 'normal' life was discussed in several interviews, for some patients, life had returned to how it had been before the surgery. Others described striving to maintain a sense of normality now that they had completed their treatment given that they had spent so much time in hospital. On the other hand, some described a sense of not being able to return to life as it had been due to the impact that LRRC and its treatment had had on them.

8.3.2.8.2 Acceptance

Many patients described a process of acceptance; accepting the lasting impact of their disease and treatment in lieu of the alternative of progression of their disease and mortality. For some patients there was no option other than learning to accept their circumstances, given the lack of alternative. Patients also identified the importance of acceptance to enable them to move forwards in their life and to enjoy life.

8.3.2.8.3 Gratitude

Gratitude was expressed by several patients in various ways, some felt grateful for being alive following LRRC and for the positive things in their life. Others described a renewed appreciation for life and gratitude for this experience changing their outlook and way of living, feeling that they had been given a "second chance". Patients expressed their gratitude towards healthcare services and the professionals who had treated them, one patient had used their experience to inform others and raise awareness of bowel cancer within their community and was grateful that they were able to draw on their own experience to do this.

8.3.2.8.4 Managing one's own health

A variety of ways in which patients managed their health following their experience of LRRC were described, these included positive health behaviours such as a healthy diet and exercising. One patient reported physical activity as being helpful in improving their mood. For some patients, how they managed their health related to their attitude, in dealing with their experiences positively or with good humour. For others, taking control and advocating for themselves in decision-making processes related to their treatment had resulted in decisions that were positive for them. A strong commitment to recovery and working towards improving mobility post-operatively was also described. One patient described trying many different treatments out with those offered by their health care system, including homeopathy, healing, colloidal silver, and oxygen hydrotherapy. Another patient reported using cannabis to help manage their pain and improve their appetite.

8.3.2.8.5 Feelings about the future

A range of positive feelings about the future were described with many patients describing taking each day at a time. Some felt confident that they could face what the future holds, having come through their experience of LRRC. Some patients described their family as being even more important to them now in terms of thinking about the future and their focus. Patients described their reasons for not worrying about the future or the possibility of re-recurrence, including it not being a good use of their time, and being motivated by their ongoing survival. A strong Christian faith was also identified as a reason for not worrying about what the future holds or one's own mortality.

Some patients described feeling negatively or worrying about the future, this included worrying about how they would manage with increasing age, particularly in relation to managing their stoma. One patient described feeling nervous given an upcoming surgery for a parastomal hernia and given their previous negative post-operative experiences. Others described feeling generally uncertain about the future.

8.3.2.8.6 The impact of co-existing long-term health conditions

Patients also described a range of co-existing long-terms health conditions, including Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus and experiencing a Cerebrovascular Accident. For one of the patients, their COPD now impacted on their day-to-day life much more than the lasting effects of LRRC as they experienced significant breathlessness on exertion which had worsened in recent years.

8.3.2.8.7 Effect of ageing

For some patients, it was difficult to distinguish whether the difficulties they experienced were due to LRRC or simply a natural part of the ageing process, these included issues such as erectile dysfunction, impaired mobility, and general fatigue.

8.3.2.9 Reflections on Adjusting to Life Following Diagnosis and During Treatment

Discussing their life now following treatment for LRRC and the impact that this experience had had, prompted many patients to reflect on their feelings at the time of their diagnosis and during treatment.

8.3.2.9.1 Feelings surrounding diagnosis and treatment

Patients described several ways in which they felt positive about their experience around the time of being diagnosed with LRRC and through their treatment, this included feeling that they had been appropriately counselled regarding the challenges they may experience. Others were satisfied with their outcome given the severity of their disease, "*I believe the surgery was very complicated, but it's all in working order. I'm really astonished with this outcome*.", particularly given that extensive surgery represented the only possibility of cure. Some patients felt that from a psychological perspective, it was easier to cope with being diagnosed with LRRC compared with their initial primary disease, feeling that it was "*less terrifying*" despite potential treatment options being more extensive.

Patients reflecting upon being diagnosed with LRRC also expressed negative feelings or aspects of their experience and the psychological impact this had on them. Following receiving their diagnosis, one of the patients described finding the period of time prior to

commencing treatment very difficult from a psychological perspective, feeling shocked. Other patients described their feelings around the time of being diagnosed with LRRC, worrying that this related to their previous decision not to have chemotherapy following surgery for PRC. Patients described the difficulties they had experienced and their lack of awareness due to colorectal cancer being perceived as taboo.

The experiences of diagnosis and treatment were also described as traumatic, with some patients experiencing a significant impact on their mood during this time. Patients reflected upon their experience of counselling prior to surgery, with some finding discovering the potential extent of the surgery shocking. One patient described initially declining surgery as they did not want to have a permanent stoma, another described worrying about the impact that the removal of their vaginal wall would have on their relationship. One of the patients felt that they had not received adequate information regarding the sexual risks of treatment, particularly in relation to vaginal atrophy. They also felt it was possible that they may have not been able to take in this information at that time due to being unwell and shocked.

Due to the specialist nature of treatment and surgery for LRRC, several of the patients had received their treatment at centres geographically distant from their home and had found this difficult emotionally. The process of recovery was also described as long and challenging, others described initially being in ‘survival mode’ following their operation before starting to process their experience and starting to deal with the lasting effects of their treatment.

8.3.2.9.2 Decisional regret and other feelings surrounding the decision to have surgery and other treatments

Some patients expressed regret in relation to their decision to have surgery or in relation to specific aspects of the treatments they had received, this included regretting the decision to have radiotherapy given their subsequent experience of vaginal atrophy, "*But, you know if they would have given me, if they would have said let's just get the surgery right now, like if I had to choose between knowing this would happen to me with radiation and risking having to have a permanent colostomy, I would have chose permanent ostomy without ever doing the radiation.".* Another patient expressed regret that they had undergone a hysterectomy due to their experiences of the menopause. Conversely, other patients described feeling pleased that they had decided to have surgery.

8.3.3 Comparative Thematic Analysis

The survivorship themes and issues identified were compared across different groups of patients including by country, gender, pattern of disease, age, margin status, and surgical versus non-surgical treatment. No significant differences in the issues reported across the countries included in the study were identified, reflecting broad similarities in their respective healthcare systems. Patients generally reported being referred to a specialist centre for their treatment for LRRC. Canadian patients reported the expense of paying upfront for stoma supplies prior to being reimbursed for a proportion of this expense. This is not the case in countries such as the UK where patients who have undergone treatment for cancer are exempt from paying for prescriptions for stoma supplies.

Excluding gender-specific issues such as sexual function and gynaecological symptoms, small differences were identified in relation to gender. None of the male patients interviewed expressed decisional regret in relation to aspects of their treatment, whereas

two female patients had experienced this. Female patients also identified a greater proportion of unmet needs within current follow-up care. In relation to pattern of disease, patients who had anterior and lateral disease reported more issues related to pain and urological function. Whereas mobility problems were most prevalent in patients with posterior and lateral disease.

In relation to age, the themes identified by patients below the age of 70 were compared to those reported by patients aged 70 or above. Most significantly, anxiety and fear of re-recurrence were only reported by patients under the age of 70, whereas none of the patients in the older age group reported this. Younger patients reported a greater number of ways in which current follow-up care could be improved, in addition to issues related to work and careers. They also reported more pain compared with older patients and issues related to fertility and treatment-induced menopause were only reported by younger patients. Conversely, patients aged 70 and above reported experiencing more issues related to ageing.

Comparison by margin status was of limited value given small number of patients with an R1 or R2 resection margin. The analysis regarding surgical versus non-surgical treatment was also limited by small numbers of patients.

8.3.4 Mapping of Survivorship Issues to the LRRC-QoL and EORTC SURV100 Measures

The survivorship themes identified were mapped to the LRRC-QoL and the EORTC SURV100 measure and are depicted in Table 8.4. When combined, the two measures cover seven (87.5%) of the survivorship themes identified, excluding Unmet Needs or

Areas for Improvement. Individually, the LRRC-QoL covers six (75.0%) of the themes and the EORTC SURV100 covers 5 (62.5%).

Table 8.4: Mapping of survivorship issues to the LRRC-QoL and EORTC SURV100 measures

Survivorship Themes and Subthemes Identified	LRRC-QoL Questionnaire	EORTC SURV100	LRRC-QoL and EORTC SURV100 Combined
Experience of Long-Term Follow-up Care	*		*
Navigating specialist follow-up care	*		*
Experiences of completion of follow-up care			
Sources of support			
Long-term procedures and interventions			
Unmet Needs or Areas for Improvement			
Unmet needs during treatment and follow-up			
Aspects of care that could be improved			
Long-Term Physical Effects of Cancer and Treatment	*	*	*
Problems related to wounds	*		*
Altered bowel function			
Pain	*	*	*
Problems related to mobility	*	*	*
Fertility and treatment-induced menopause		*	*
Vaginal symptoms	*	*	*
Urinary symptoms	*		*
Generalised symptoms		*	*
Living with a Stoma, Urostomy or Other Urinary Device	*		*
Problems with the stoma	*		*
Impact of a stoma on daily life			
Feelings about the stoma	*		*
Impact of a stoma on social life and relationships			
Managing a urostomy or other urinary device	*		*
Long-Term Psychological Impact	*	*	*
Feelings about self and body image	*	*	*
Anxiety and fear of re-recurrence	*	*	*
Impact on mental health		*	*

Impact on Sexual Function and Intimate Relationships	*	*	*
Sexual interest	*	*	*
Sexual function	*	*	*
Feelings surrounding sexual function		*	*
Impact on Daily Life: Relationships, Work, Finances, and Recreational Activities		*	*
Impact on relationships		*	*
Impact on social life		*	*
Impact on hobbies/travel		*	*
Financial impact		*	*
Impact on work or career		*	*
Retirement			
Managing at home		*	*
Feelings Surrounding Life Now, Adapting, and the Future	*	*	*
Life returning to normal or a 'new normal'			
Acceptance			
Gratitude		*	*
Managing one's own health		*	*
Feelings about the future	*	*	*
Impact of co-existing long term health conditions			
Effect of ageing			
Themes covered	**6 (75.0%)**	**5 (62.5%)**	**7 (87.5%)**
Subthemes covered	**14 (35.9%)**	**20 (51.3%)**	**26 (66.7%)**

8.3.5 Analysis of HrQoL Outcomes

Ten patients, 8 male and 2 female, returned the LRRC-QoL questionnaire, their responses are detailed in Table 8.5. The mean overall HrQoL score was 40.70 (SD 11.81), denoting relatively good overall HrQoL, though higher than the mean baseline score of 36.85 (SD 9.10) reported in chapter 7. The scores for the scales indicate a low burden of symptoms including pain (mean score 5.40, SD 2.17), urinary symptoms (mean score 2.60, SD 0.97), lower limb symptoms (mean score 6.20, SD 2.66), stoma-related issues (mean score 4.10, SD 1.91), and urostomy or urinary device related issues (mean score 1.20, SD 2.57). The mean score of 2.50 (SD 1.43) for the Sexual Interest scale indicates that patients reported low levels of sexual interest or pain during sexual activity. The gender-specific Sexual Function scale scores suggest a higher degree of symptoms in men (mean score 6.13, SD

1.36) compared with women (mean score 3.00, 1.41), though a statistical comparison was not undertaken given the small number of patients completing the measure. The mean score of 8.80 (SD 4.59) for the Psychological Impact scale indicates a moderate level of psychological issues were reported. The Healthcare Services scale mean score of 9.80 (SD 2.04) denotes relatively positive experiences.

Table 8.5: LRRC-QoL responses

LRRC-QoL Scale	Mean Scores	SD	Number of Patients Completing the Scale	Possible Score Range
Overall HrQoL Score	40.70	11.81	10	18-96
Pain	5.40	2.17	10	3 - 12
Urinary Symptoms	2.60	0.97	10	2 - 8
Lower Limb Symptoms	6.20	2.66	10	3 - 12
Stoma	4.10	1.91	10	0 - 8
Urostomy	1.20	2.57	2	0 - 12
Sexual Interest	2.50	1.43	10	2 - 8
Sexual Function				
Female	3.00	1.41	2	2 – 8
Male	6.13	1.36	8	2 - 8
Psychological Impact	8.80	4.59	10	4 - 16
Healthcare Services	9.80	2.04	10	3 - 12
Single Items				
Question 9	1.00	0.00	1	0 – 4
Question 10	1.50	0.97	10	1 – 4
Question 28	2.20	1.14	10	1 - 4

8.3.6 Researcher Reflective Log

Overall, I found facilitating the interviews to be a real privilege as it allowed me to gain a better understanding of the personal experiences of patients in a way which is difficult to gather during clinical encounters given the time constraints. Developing my skills as a

qualitative interviewer was a learning process, I felt that I am proficient in skills such as developing rapport with patients and showing empathy, but nevertheless found several aspects challenging and identified areas for improvement. These included learning to keep questioning open to allow the participant to guide the interview and not my pre-conceptions of the issues I felt were relevant. I also found some of the interviews challenging from an emotional perspective as patients shared some of their most difficult life experiences with me. My background as a clinician may have made patients feel more comfortable speaking to me about their experiences given a degree of professional trust. I suspect that my gender may have also put some patients, particularly female patients, at ease in relation to discussing sensitive topics such as sexual function. Conversely, my gender and age may have been a barrier to some patients. Participants may also have found it difficult to share negative healthcare experiences due to me being a 'member of the establishment'. Other researchers involved in conducting interviews internationally (JvR and SW) also reported feeling privileged to have heard the experiences of these patients during the in-depth interviews.

Transcribing the interviews myself was helpful as I was able to immerse myself in the content, allowing for reflection and for me to critique my interview technique; identifying missed opportunities or cues, more pertinent lines of questioning or how I could have better phrased a question. During the analysis process, I enjoyed utilising the framework method as the data is represented visually during the interpretation process, which suits my personal learning and processing styles. I also felt this approach worked well with the international, collaborative approach to recruitment as it was flexible and suited to collaborative working during the analysis process. My clinical background and knowledge of the themes which arose from the development of the LRRC-QoL, is likely to have influenced the analysis and the lens through which I coded the data, informed by

the bio-psycho-social approach I had learned at medical school (321), and my own experiences from clinical practice. I tried to use this to my advantage to inform the analysis, whilst also ensuring that the themes identified reflected the experiences and feelings of the patients interviewed. I did this by returning to the transcripts frequently to ensure they were represented in the analytic framework.

8.4 Discussion

The eight major survivorship themes identified in this study portray the long and lasting impact of LRRC and its treatment, with patients experiencing ongoing physical effects, with an impact on their daily lives and their long-term psychological function. The study demonstrates that longer-term survivors of LRRC continue to experience similar issues to those previously described by patients who are closer to diagnosis (106, 143). Despite this, patients were generally accepting of their 'new normal' and had adapted well, which is evident in the relatively positive overall HrQoL scores from participants completing the LRRC-QoL. An important finding of the study was that the majority of survivorship issues identified mapped to the LRRC-QoL questionnaire, indicating that it can be used to assess survivorship and HrQoL in this specific group of patients.

The experiences of patients with LRRC up to two years following diagnosis or treatment have been previously explored from both a survivorship and HrQoL perspective. Lim et al.'s survivorship work in patients with advanced or recurrent colorectal cancer identified themes regarding the impact of protracted, complex illness, including side effects, stomas, and the loss of identity, compounding and interacting effects of treatment, and the unpredictability of survivorship (143). In relation to HrQoL themes, the LRRC-QoL

conceptual framework identified symptoms, sexual function, psychological impact, role and social functioning, and future perspective (106). The themes identified in this study by patients who were a median of five years post-treatment share many similarities with both the survivorship and HrQoL issues previously described in patients closer to diagnosis, demonstrating the long and lasting impact of experiencing LRRC and its treatment. The study offers the first qualitative insights into the lived experiences of longer-term survivors of LRRC and highlights the distinctiveness of this patient group. These results do not reflect the growing body of evidence regarding survivorship in primary malignancies, where longer-term survivorship issues are reported to be different to those experienced by patients during treatment (119).

Healthcare experiences have also been explored in patients with LRRC up to two years, identifying themes including trusting the system and professionals, early experiences influencing later perceptions, the benefits of MDT care co-ordination, feeling lost in follow-up, gaps in responsibility for survivorship care, and perceptions of psychosocial support (144). Healthcare service delivery and utilisation are represented in the LRRC-QoL conceptual framework (106) and were identified as an important component of the experiences of the long-term survivors included in this study. This included the identification of several unmet needs and areas for improvement within current survivorship care. These findings have significant repercussions given their generalisability; they highlight aspects of care which could be improved across a broad international platform. The study also advances long-term HrQoL assessment in LRRC from a methodological perspective through identifying the most appropriate measures for use in this setting.

Long-term survivorship in LRRC has been poorly reported to date, however there are a small number of studies regarding long-term HrQoL; suggesting an initial reduction in HrQoL outcomes after surgery, followed by a sustained return to or improvement beyond baseline by 6-12 months (146, 147). As identified in chapter 2 of this thesis, there are limitations to current HrQoL reporting in LRRC, particularly in relation to the measures being used. In terms of the evidence for survivors of 3 years or longer, the FACT-C and SF-36 have been used almost exclusively in this context (146, 147), though neither have been validated for use in LRRC. The mapping of the survivorship issues identified in this study to the LRRC-QoL demonstrate its relevance as a measure of HrQoL in longer-term survivors, supporting the extension of its use to this group of patients.

Where survivorship care is concerned, there have been no published descriptions of dedicated survivorship care interventions or clinics for this specific group of patients. Standard follow-up care for patients with colorectal cancer comprises of surveillance for recurrence (322) and monitoring for long-term effects of treatment (81). ESMO guidelines for rectal cancer follow-up advocate late effects/survivorship clinics particularly for patients who have received pelvic radiotherapy (81). This applies to many patients with LRRC, though it is difficult to know the extent to which this aspect of follow-up and survivorship care is being delivered within current clinical practice. This is reflected in the unmet needs reported in this study, with female patients in particular reporting unmet needs in relation to their sexual function. There are several barriers to the delivery of aftercare regarding sexual function which may contribute to these findings, including time constraints within clinic appointments preventing detailed discussions of sexual function and its impact on patients and their relationships (323). Clinicians may not feel equipped to address both the physical and emotional aspects of sexual function (323-325), or may assume a lack of relevance based on patient characteristics such as age

(324). Additionally, the majority of general surgical consultants are male (326), which both patients and clinicians may perceive as a barrier to discussing female sexual function (323).

Communication was also highlighted as an important aspect of care which could be improved both in this study and previously by the ACPGBI IMPACT initiative (15). The highly specialist nature and complex delivery of LRRC management, often involves referral to specialist centres or provision of aspects of treatment, such as oncological or surgical treatment and scans, across different centres. This necessitates good communication between healthcare practitioners and patients in addition to between teams working in different specialties or at different institutions. Lim et al. have previously highlighted how the complexity in care for patients with advanced colorectal cancer can lead to confusion from a patient-perspective regarding which clinician is responsible (144). They suggest the implementation of survivorship care plans (327), or survivorship clinics to help overcome some of these barriers (144), however there is currently limited evidence of their utility in this setting.

There are some important strengths of this study, including the robust qualitative methodological approach employed, utilising a framework method for thematic analysis. Selection of this approach was carefully considered and felt to be best suited to the aims of the project and plans for collaborative, international working. Furthermore, all interview facilitators had either received training in qualitative methods or were experienced qualitative researchers. The major strength of the study was the multi-centre, international approach to recruitment, with a view to identifying issues which would be generalisable across several countries. The LRRC-QoL conceptual framework identified

significant similarities in the issues reported by patients recruited from Leeds and Sydney (106), therefore the generalisability of this framework is likely to extend to longer-term survivors. The approach to international recruitment and analysis was carefully planned with close collaborative working to ensure conceptual equivalence was maintained and not lost in translation. The study design included flexibility in the setting for the interview to suit both patients and research teams. The English-speaking interviews were conducted remotely, enabling recruitment to continue during the COVID-19 pandemic. This also facilitated recruitment of patients geographically distant from the research team and patients with limited mobility who may be less able to travel to attend an interview. Non-English language interviews were all held in person. Current practice within the field of qualitative research, particularly in light of the COVID-19 pandemic, suggests that there are no significant differences in data richness between approaches (328).

One of the major limitations of the study is the use of the LRRC-QoL conceptual framework to inform the interview topic guide, which may have influenced the themes identified. However, the two main interviewer facilitators (NM and SW) did not feel that this was significant, and that the majority of discussion was generated by the more open questions at the beginning of the interview which did not relate to the LRRC-QoL. Other limitations include the lack of diversity in the patients recruited, with the majority being Caucasian in origin. Recruitment was also undertaken in high-income countries only, meaning patients from low- and middle-income countries are not represented. The low response rate to the LRRC-QoL questionnaire limits the ability to draw meaningful conclusions from this data and likely occurred due to its administration following the interviews, meaning participants may have been less likely to remember to complete it. This approach was taken to avoid responses to the interview being influenced by the LRRC-QoL. The prolonged recruitment timeframe for the study and significant number

of patients who consented into the study and were later found not to meet the eligibility criteria, reflect the challenges encountered during study delivery. Some centres approached to take part in the study experienced difficulties in identifying patients due to a lack of prospective registries. Where international non-English language centres were concerned, sites were only invited to participate if they had experience in conducting qualitative research and were able to facilitate interviews, limiting the number of sites. In relation to the centres who participated and recruited to the study, there were difficulties in identifying patients who remained disease-free once they had completed follow-up. Some patients were recruited to the study and found to have developed metastases/re-recurrence, having received treatment at their local hospital without the specialist centre's knowledge.

This study has important implications regarding the future of HrQoL assessment and survivorship care in long-term survivors of LRRC. Prospective HrQoL reporting utilising the LRRC-QoL, a robustly developed and validated disease-specific measure, could offer significant value in increasing understanding of the long-term impact of LRRC and its treatment on HrQoL. Administering the LRRC-QoL alongside the EORTC SURV100 has additional benefits in capturing more generic cancer survivorship issues and enabling comparison across patient groups. The only theme not represented in these measures was Unmet Needs or Areas for Improvement. Unmet needs are described as the disparity in the issues patients experience and the resources or care they require (329, 330), and can be measured using the Short-Form Survivor Unmet Needs Survey (SF-SUNS) (330). Areas for improvement in patient experiences of healthcare services could also be captured by PREMs, though there are currently no existing PREMs for use in this specific context. In recent years, the integration of PROMs within follow-up care settings has enabled clinicians to identify and target patients in need of additional support, resulting

in improved HrQoL outcomes (130, 131). The LRRC-QoL could also be used as a screening tool within LRRC follow-up care to identify patients who would benefit from interventions, such as support managing treatment effects, or access to psychological support services.

Long-term survivorship care for patients following treatment for advanced pelvic malignancy, including LRRC, is likely to represent an important area of interest as the number of survivors continues to rise. There are numerous potential approaches that could be utilised to address the unmet needs and issues highlighted in this study. Support in relation to sexual function could be improved through the introduction of routine access to sexual health practitioners or counselling within standard LRRC follow-up care (331, 332), Alternatively, training could be offered to clinicians, such as surgeons, oncologists, and specialist nurses, to facilitate high-quality delivery of this important aspect of survivorship care for patients with LRRC (333, 334). Where communication is concerned, several patients identified their dedicated specialist nurse as a significant source of support during their treatment, follow-up care, and beyond. Ensuring all patients with LRRC have access to a dedicated specialist nurse may help them to feel more supported in navigating their treatment and follow-up pathways. Currently only 26.2% of MDTs across Great Britain and Ireland report having a dedicated advanced colorectal cancer nurse specialist (11). Other options could include access to virtual survivorship care interventions (335), which could particularly benefit patients living far from their treating centre. This study also highlighted the increased fear of re-recurrence in younger patients, confirming the findings of Lim et al. (142). Further work to explore this issue could facilitate the development of strategies to better support patients experiencing fear of re-recurrence or death anxiety.

In relation to delivering these improvements in survivorship care, further work is required to establish the gaps in current survivorship care at local, regional, and national level, with a view to developing strategies to address them. Investigating unmet care needs and areas for improvement within survivorship care at a local and regional level would enable the development of interventions or pathways that satisfy the needs of the local population and healthcare system. At a national level, the ACPGBI IMPACT study is currently underway and will help to more clearly define the issues to address in current care pathways for patients with advanced colorectal cancer within the UK. Given the highly specialist nature of LRRC management, securing funding for additional services may be challenging. Collaboratives such as UK PEN could help advocate for improvements in survivorship care for patients with LRRC in the UK, alongside PelvEx internationally. Most importantly, the development of any targeted survivorship interventions or changes to current LRRC survivorship care should be undertaken with input from patients and other key stakeholders within the specialist MDT.

8.5 Conclusion

The wide range of survivorship issues identified in this study reflect the complexity of LRRC and its management, establishing that patients continue to experience similar issues to those described in patients closer to diagnosis or still receiving treatment (106, 143). This has important implications and supports the use of the LRRC-QoL to assess HrQoL in long-term survivors of LRRC. There are several unmet needs which could be addressed to improve survivorship care for those experiencing LRRC, including improved communication and better aftercare regarding sexual function.

Chapter 9 The Challenges of Setting Up a Prospective, International, Multi-Centre Research Study

9.1 Introduction

As described in chapter 1, LRRC has become a relatively rare occurrence. Despite this, it remains an important area for research given its significant impact on both patients, in whom it frequently causes debilitating symptoms (106), and on healthcare services, given the financial implications of radical surgical management (47). Given its low incidence rates, researchers must consider this in their approach to study design and delivery; collaboration takes on crucial importance when conducting research in rare disease areas, where shared experience is essential to accruing greater understanding. The benefits to be gained from international collaborative research in LRRC have been demonstrated by initiatives such as the PelvEx Collaborative; through which specialist centres have pooled their outcome data leading to a significant improvement in outcome reporting in patients undergoing exenterative surgery, including patients with LRRC (35).

This project was designed as an international study for several reasons. One of the key aims of the project was to undertake cross-cultural validation of the LRRC-QoL questionnaire to enable its use on an international platform and therefore international collaboration was essential to achieve this. Furthermore, the low incidence of LRRC meant that meeting the required sample size to validate the questionnaire was unlikely to be feasible if recruiting from UK centres alone. However, delivering a prospective, international, multi-centre project comes with its own challenges and there are many important factors to consider from study design through to delivery. Some of the

difficulties involved in setting up and running such studies have previously been reported, including the diverse regulatory approvals required in different countries and at different sites, the negotiation of contracts for site setup, navigation of different time zones and language barriers (336, 337). The International Surgical Trials Toolkit was developed by the University of Leeds Clinical Trials Research Unit (CTRU) to improve the efficiency of setup and conduct of international surgical trials and contains key areas for consideration in relation to study design and implementation (338). This toolkit was referred to frequently throughout the process of setting up and running the LRRC-QoL study, particularly in relation to finances, translation, and contracts.

The timing of the delivery of the LRRC-QoL study brought additional challenges to overcome in the form of a global pandemic and a period of considerable uncertainty surrounding Brexit (339). This chapter discusses the challenges encountered during the setup and delivery of this PhD project and the lessons learned. The issues are presented in keeping with the timeline in which they were encountered, from gaining ethical approval, financial considerations, translation, and legislation, through to the COVID-19 pandemic, site setup, and recruitment.

9.2 Ethical Approval

Gaining ethical or regulatory approval is the first step in setting up research sites and is essential prior to commencing recruitment. In the UK, the Health Research Authority (HRA) manages ethical approvals centrally which are granted by Research Ethics Committees (REC). Once HRA and REC approval for a study is in place, Research and Development (R&D) departments for each participating NHS site in the UK must also

grant local approval for the study. The processes for international ethical approvals are variable, for instance the United States of America (USA), uses an Institutional Review Board (IRB) system where each participating centre requires approval from its own IRB. In Europe, ethical approvals must adhere to the European Union (EU) Clinical Trials Directive of 2001 (340) which has been heavily criticised for introducing increasing trial costs, reducing the number of new trials and has resulted in a lack of harmonisation in the interpretation of the directive in different countries (341). In recent years, there have been efforts to improve this through the introduction of new legislation in the form of the Clinical Trials Regulation, enacted in 2014 and taking effect on the 31st January 2022 (342). This legislation includes the introduction of the Clinical Trials Information System (CTIS), which aims to centralise the approval processes for clinical trials in the EU. The CTIS represents a promising initiative that may positively affect the delivery of multi-national clinical research within the EU; however, it will only be possible to assess its impact over the course of the coming years.

The multiple regulatory and ethical approvals required represent one of the main challenges in conducting international, multi-centre research and are a common experience for researchers working in this field (336, 337). Collating each approval from a REC, IRB or local committee can be time-consuming for both local research co-ordinators and central research teams; often demanding different forms or reformatted versions of similar documents to satisfy local requirements. The LRRC-QoL study was a collaborative study with 41 sites across 17 countries. There were 15 sites in the UK and as described, the process for setting up these sites involved gaining REC and HRA approval followed by R&D approval to allow each site to commence recruitment. The 26 international sites largely required individual hospital or regional ethical approvals such as IRB approval for the American sites. One site based in Chapel Hill, USA, suggested

the use of a Reliance Agreement as an alternative to a full IRB approval. A Reliance Agreement is put in place between the participating site and the University of Leeds, confirming that the participating "relying" institution may rely upon the University of Leeds as the Reviewing Institution for review and continuing oversight of its research. This approach had not previously been applied by the University of Leeds and led to delays in the development of a suitable agreement for these purposes due to a lack of familiarity with the process. Sites in other countries, such as those in the Netherlands and India, reported a similar process to the UK, wherein a national approval was required followed by a local/hospital ethical board approval. The process and timelines for site setup will be discussed further later in this chapter.

9.3 Financial Considerations

The inclusion of international sites was present in the grant application for the study with an initial strategy to include four international centres and to develop a validated LRRC-QoL questionnaire in four languages, including English. As the project continued, the number of international centres grew to 26 and a total of 14 languages including English. However, the LRRC-QoL study is a charity-funded project and as such, resources were finite. One of the main expenses during the project was the cost of translation, for both the LRRC-QoL questionnaire via a forward-backward approach and for study documents such as patient information leaflets and consent forms. For this reason, it would not have been possible to include any additional languages in the project than those described within the constraints of the resources available.

Finances also presented a challenge given the limited ability to fund clinical collaborators for their time spent working on the study. The EORTC QLG provide payments per patient for questionnaire development. EORTC provide a payment of €50 for completing a single questionnaire, €100 for a patient completing two questionnaires, €150 for completion of three questionnaires and €100 for face-to-face interviews. The funding for the LRRC-QoL study did not include per patient payments, however, the project's charity funding meant that it was eligible for National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio-adoption in the UK. CRN portfolio-adopted studies can benefit from provision for Research Part B costs which include the cost of local study trial-co-ordination and management, data collection, obtaining ethical approval and the Principal Investigator's time (343). These benefits were not applicable to international sites and discussions relating to the financial implications of running the study at international sites occurred during the setup of several centres. In the case of the majority of participating international sites, research fellows were able to help with the delivery of the study without the requirement of additional funds. The study funding included allocations for expenses such as postage of the questionnaires, which could be transferred to participating international sites to reimburse them for such expenses. The research agreement, described in greater detail later in this chapter, included a clause related to compensation for costs incurred; "*The Lead shall pay to the Site, Legitimate Expenses that have been incurred as part of its involvement in the Study. Any such expenses must be approved in writing, in advance, by the Study Chief Investigator*."

In the case of sites in Milan, Italy and Sengkang, Singapore, participating teams highlighted the financial implication of clinicians dedicating their time to the delivery of the study. The study budget did not allow for re-compensation of the estimate for the total funds required for the clinician time that would be necessary to deliver the study at these

centres. Participating clinicians were understanding of the financial limitations and given their support of the aims of the project agreed to accept a one-off payment upon the recruitment of 10 patients to the cross-cultural adaptation interviews. Such payments to international sites were not included in the original funding application and were procured by redistributing other aspects of the budget that were no longer required, such as funds for teleconferencing given the widespread availability of videoconferencing technology such as Microsoft Teams and Zoom.

9.3.1 Lost in Translation

In addition to the financial implications of translation, there were also challenges related to delivering a project in 14 different languages and 12 time zones. A company which had previously been used by the University of Leeds, receiving good feedback and who offered a competitive rate, were engaged for the translation of the patient information leaflets. The team based in Bordeaux, France, reported that the translation of the patient information leaflet was too literal and did not appropriately convey information regarding the study to potential participants. This led to delays in setting up the study as the local team were required to amend the patient information leaflets.

Furthermore, research regulations vary internationally, with some sites reporting that the volume of information regarding data protection the inclusion of which is mandatory in the UK was not required by their local regulations. The UK ethical approval requires inclusion of specific information regarding the categories of personal data being collected, the period of time it will be held for, the potential for anonymised data to be used in future research studies, the data subject's rights under General Data Protection Regulation (GDPR) and details to contact the Data Protection Officer and Information

Commissioner's Office should participant's wish to raise a complaint regarding the handling of their personal data (344). This information is not necessarily required for inclusion in the patient information leaflets by ethical approval boards at individual sites internationally such as Bordeaux, France and Barcelona, Spain.

9.4 Navigating International Legislation

From a legal perspective, research or data processing agreements are required to be in place between the organisation sponsoring a research study and any organisations participating in the research. In the UK, a document called the Organisation Information Document (OID) for non-commercial studies acts as a data processing agreement between the sponsor and participating NHS sites (345), however an OID cannot be used as a research agreement for sites out with the NHS. The International Surgical Trials Toolkit describes two options for research agreements with international sites, the first option being to create agreements between the sponsor and each international site, the second option being to create agreements between an international spoke and for the spoke to create contracts with local research sites (346). In the case of the LRRC-QoL study, the former approach was taken, and an agreement put in place between the sponsor, the University of Leeds, and each participating international site. The Toolkit describes some common areas for disputes with this approach (346), most of which were encountered during the process of putting in place and signing the agreements.

9.4.1 Issues Related to Data Sharing Agreements

9.4.1.1 Jurisdiction of Agreement and Governing Law

Agreeing the court of jurisdiction that will govern the agreement, can be a point of contention, with each party generally preferring that their local national laws and courts govern the agreement. In the case of the LRRC-QoL study, given that the University of Leeds is UK based the preference and original wording of the agreement is that it be governed by English Courts. Several international sites, including Cleveland, USA, Vancouver, Canada, Aarhus, Denmark and Rotterdam, the Netherlands proposed changes to the agreement stating that their local laws and courts govern, in all cases a resolution was reached through remaining silent on jurisdiction. This approach is also advised in the International Surgical Trials Toolkit (346).

9.4.1.2 Warranties, Indemnity, and Insurance Clauses

The LRRC-QoL agreement included a cap on liability of £5,000, sites in Vancouver, Canada and Cleveland, USA, initially requested that this be removed on the grounds that they were not able to cap liability under their indemnity. The University of Leeds recognised that under English Law, there could not be a cap on liabilities for events such as death or personal injury due to negligence, with the agreement stating that the liabilities will not extend to punitive, indirect, or consequential losses. This strict legislative framework exists to safeguard patients in Clinical Trials of an Investigational Medicinal Product (CTIMPs) and has evolved following the introduction of key European legislation, the European Council directive in 1965 (347), in response to the harm caused by thalidomide. Though these safeguarding processes are undeniably important, the same strict regulations are applied to questionnaire studies, which pose much lower risk or no risk of harm to patients. A virtual meeting was held between the contract teams at both the University of Leeds and the Cleveland Clinic during which it was agreed that the cap

could remain in place, provided the amount was stated in US dollars, given that the study itself presented low potential for damages.

9.4.1.3 Intellectual Property Rights

The data sharing agreement stated that the University of Leeds would hold the intellectual property rights to any results from the study. The legal department of the site in Rotterdam, the Netherlands, proposed a change to the agreement to state that both parties would be co-owners of the study results, this was not deemed appropriate by the sponsor and following further discussion an agreement was reached. The final agreement stated that the Lead site, namely the University of Leeds, would own any intellectual property generated from the study and the research site's ownership of any background intellectual property owned or controlled prior to the study or generated outside the scope of the study, would not be affected. The site in Vancouver, Canada, proposed that any intellectual property created in the course of the study would be owned by the University of Leeds and "*used solely for the conduct of the Study*". The University of Leeds, for the reasons that their intellectual property rights must be unencumbered, deemed this unacceptable.

9.4.1.4 Publication Rights

A publication policy was included in the data sharing agreement stating that all research staff who recruit participants into the study would be recognised as collaborative authors on subsequent publications, this was accepted by all participating sites.

9.4.2 International Data Transfer and Brexit

The transfer of personal data is governed by GDPR in EU law; GDPR was implemented in 2018 with a view to giving individuals control over their personal data and simplifying data transfer within the EU (348). The Data Protection Act (DPA) 2018 (349) is the UK's implementation of GDPR, however, following the EU referendum of 2016, Britain was likely to leave the EU whilst the LRRC-QoL study was underway. The DPA classifies countries outside of the UK as either adequate or non-adequate in relation to the transfer of personal data. The impending Brexit brought a degree of uncertainty regarding potential legal regulations for the transfer of personal data between EU nations and the UK following the end of the Brexit transition period on 31st December 2020.

Navigating the Brexit process whilst enabling recruitment to continue at EU sites was a major concern in the design of this project. Legal advice was therefore sought from the University of Leeds contract team, leading to the inclusion of Standard Contractual Clauses for the transfer of personal data (350) in the data sharing agreements, which would allow personal data transfer to continue post Brexit. Following Brexit on the 1st January 2021, a treaty agreed between the UK Government and the EU allowed for personal data transfer from the EU to the UK to continue, either until adequacy decisions had been adopted or for up to six months. On the 28th June 2021, the UK Government announced that the EU had formally recognised the UK's data protection standards as adequate (351). At this point, the patient information leaflets (PILs) for all participating EU sites were updated to include information in relation to Brexit and the transfer of their personal data to the UK. Fortunately, these changes were viewed as minor from an ethical approval perspective at all participating EU sites and introduction of the amended PILs did not result in delays to recruitment.

The inclusions of the Standard Contractual Clauses meant that the agreement could also be used for countries deemed inadequate by the DPA such as the USA. However, approval of these agreements in some cases required several months of discussions and amendments to reach an agreement that was acceptable to both parties from a legal perspective. Some sites in these non-adequate countries, Vancouver, Canada and Cleveland, USA, voiced their concerns regarding agreeing to comply with GDPR laws which they were not subject to under their own legal jurisdiction, eventually this was resolved following additional meetings to reach phrasing which was mutually agreeable. In the case of the Cleveland Clinic, the final agreed phrasing stated that the research site would consent to comply with the Standard Contractual Clauses but only under the circumstances of data transfer from the University of Leeds to the research site using the CTRU Secure File Transfer Service, in line with the planned study activities detailed in the protocol.

9.5 Conducting International Research during a Pandemic

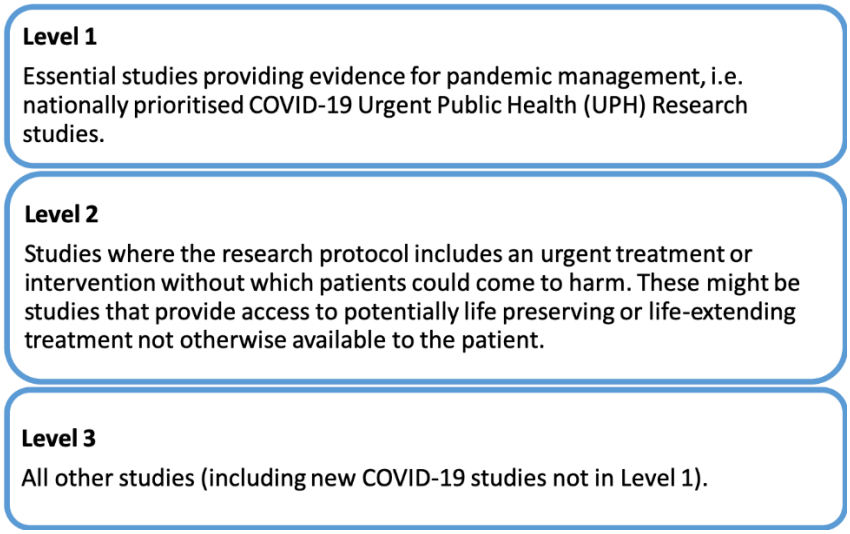
9.5.1 Impact of COVID-19 in the UK

Conducting an international, multi-centre study amid a global pandemic has at times been undeniably challenging. The pandemic has in many ways seen the delivery of international studies with an unprecedented rapidity; initiatives such as the COVIDSurg Collaborative have demonstrated the ability to take an international study from conception to publication in a space of a few months (352). Several factors have contributed to the ability to deliver research rapidly. In the UK, the HRA developed new fast-track services for REC review and approvals for COVID-19 studies that would produce interim or final results published within a year or were funded through the NIHR

call for COVID-19 research (353), meaning studies would be reviewed within 72 hours of submission. A fast-track transparency process was also developed to ensure information regarding approved studies are published on the HRA website. The publication process was aided through increased focus on rapid peer review, particularly for COVID-19 related research (354).

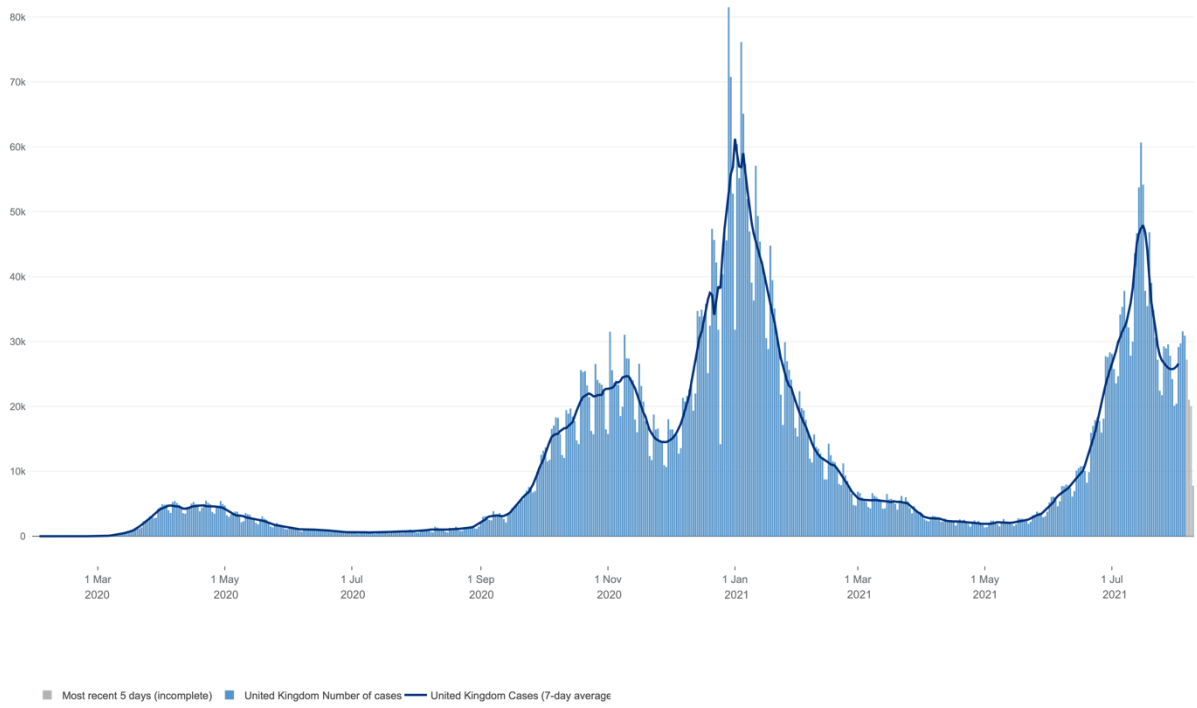
However, researchers working on non-COVID related research have understandably not experienced these advantages. During the first peak of COVID-19 cases in the UK, setup for new non-COVID studies was halted entirely from the 23rd March 2020; consequently, this project was placed on hold from March to August 2020. Gradual resumption of paused studies and new study setup was permitted from May 2020 using a prioritisation system shown in Figure 9.1 and the study received full REC and HRA approval at the beginning of October 2020. Regarding site setup, the study fell into level three and was therefore at a lower priority, meaning it was not prioritised for site R&D approvals. R&D departments understandably focused their attention on COVID-research and therefore had limited resources to devote to lower priority studies. During this time, many researchers and nurses returned to full-time clinical work to help support the additional strain placed on the NHS, this also limited sites' capacity to setup non-COVID research studies. These experiences are also reflected in those reported by clinical trials setting up during this time (355). Arguably, the stresses and demands placed on clinicians and research staff meant that non-COVID research was simply not at the forefront of their minds.

Figure 9.1: Prioritisation framework for restarting NIHR research activities (356)



The second peak of the COVID-19 pandemic occurred from late October 2020 (see Figure 9.2), with a UK national lockdown from 5th November to the 2nd December 2020 followed by a further lockdown commencing on the 6th January 2021. Restrictions in England started to lift gradually from the 8th March to 19th July 2021. Though study setup was able to continue during the second/third peak of COVID cases, several centres reported that their research staff, particularly specialist research nurses had again been redeployed in response to the pandemic, which further affected the R&D approval processes at several UK sites particularly in the early months of 2021.

Figure 9.2: UK COVID-19 cases by specimen date, graph published by Public Health England (357)



Despite falling into a lower-level priority, the study had several favourable characteristics that enabled it to proceed. The design of the study was based on a patient identification centre model with a view to reducing the workload for clinical and research teams. No additional face-to-face patient contact was required during study delivery meaning participants would not be put at increased risk of COVID-19 transmission, which was particularly important in this vulnerable patient group. Furthermore, clinical trainees were advised to remain in research posts during the second peak rather than return to full-time clinical practice as many had done in March 2020 and several UK centres looked favourably on the study given it formed the basis of a PhD thesis. Increases in virtual working practices also had a positive impact on the study, meaning it was possible to access geographically distant MDT meetings virtually; enabling the researcher to help teams identify eligible patients, this also improved engagement with clinical teams at sites where this was possible.

9.5.2 Impact of COVID-19 Internationally

Delays in usual study processing and approval times due to the pandemic were reflected in centres internationally, with several sites reporting that gaining ethical approval was taking much longer than usual. A number of countries globally were particularly badly affected by the COVID-19 pandemic, including India. India experienced a severe peak in cases during spring 2021 and setup at sites in Srinagar, Hyderabad, and Mumbai, and Karachi, Pakistan, was paused and the essential training for workstream I interviews was postponed. Recruitment commenced in India and Pakistan in August 2021. Brazil also experienced a high rate of COVID-19 cases, which had a significant impact on their national ethical approval process for the study, with final approval for the site in São Paulo granted in March 2022. Italy was badly affected by the pandemic during spring 2020, however at the point of setting up Milan as a site in early 2021, the COVID caseload was much lower and had less of an impact on the study, this was also the case in St. Petersburg, Russia. The sites in Australia were comparatively more affected by COVID-19 in 2021 when the numbers of cases rose prompting further local lockdowns in Sydney and Melbourne. Usual practice at the site in Sydney would be to recruit patients to research studies during their initial clinic appointment, this was more difficult with clinic appointments being held either virtually or via telephone due to the pandemic and given that members of staff had been redeployed. Further delays were also experienced in setting up the Australian sites in relation to the previous approval for the original LRRC-QoL development (108), the study was planned to be approved as an amendment but this was not possible as the maximum time limit to do so was exceeded. A full ethical application was therefore required at each site, approval was granted in November 2022 for the site in Adelaide. Following this, the sites in Melbourne and Sydney were added

on as sites to the Adelaide approval, with final local approvals being granted in June and July 2023.

The ethical approval process in Dublin, Ireland, was significantly affected by the COVID-19 pandemic, the study was due to be discussed by their Ethical Committee in December 2020, however this was postponed until April 2021, following review at this meeting, minor revisions were required but further delayed by lack of staffing to enable committee meetings. Final approval for the study was never granted. Minor delays were also experienced in the approval process for the study in Gothenburg, Sweden and ethical approval was granted in April 2021, with recruitment commencing in August 2021 due to the availability of the research team to conduct the interviews.

Other sites were less directly affected by the pandemic in terms of setup and study delivery. The first international site to open to recruitment was Bordeaux, France, though delays were experienced in relation to amending the patient information leaflets as previously described. Barcelona, Spain, was the second site to open to recruitment internationally. The process of gaining ethical approval was relatively timely, however, COVID-19 presented additional difficulties during the recruitment process, the team at site reported that it had a negative impact on patients choosing to participate in the study and the availability of staff to deliver the study. Sengkang, Singapore, was similarly relatively quick to setup with the main cause for delay being agreement of financial reimbursement, however, recruitment was slow due to difficulty in identifying patients who met the eligibility criteria for the study. Another site to progress through setup quickly was Sacramento, California, though again, recruitment was affected by difficulty in identifying patients meeting the eligibility criteria. Both sites in the Netherlands;

Eindhoven and Rotterdam, progressed through study setup quickly with COVID-19 having relatively little impact, the main issue encountered during this process being in relation to data transfer and Brexit. The delays encountered at other sites, including Christchurch, New Zealand, Aarhus, Denmark, Vancouver, Canada, Cleveland and Chapel Hill, USA were largely related to issues in finalising the data sharing agreement. However, issues related to the pandemic, including illness, redeployment and staff adapting to working from home all compounded these delays.

9.6 International Conflict

The Russian invasion of Ukraine in February 2022 also had an impact on the study, the team based in St. Petersburg, Russia reported recruiting 12 patients to the study, however this data was never transferred to the research team and the last contact occurred in May 2022. Following this there was no response to any further correspondence which may have been due to the conflict. The University of Leeds also advised against collaboration with Russian research institutes from March 2022 and so no further attempts were made to pursue transfer of this data (358).

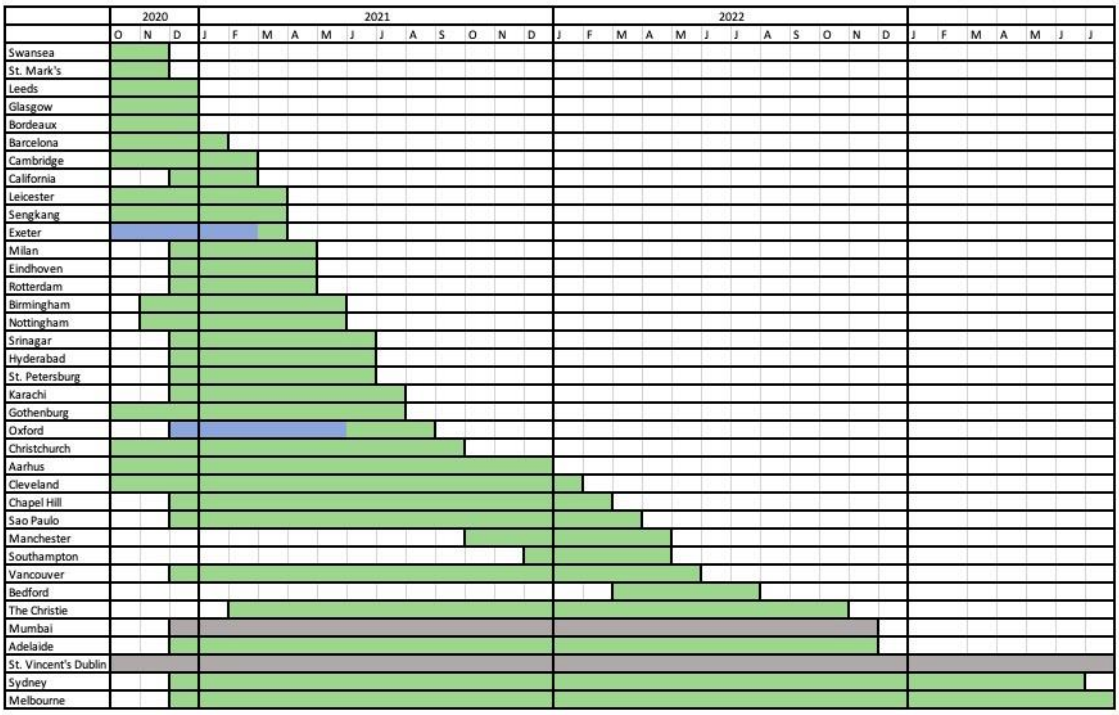
9.7 Site Setup

In relation to the LRRC-QoL study, the timeframe required for setup at UK sites was defined as the interval between the local information pack being circulated to the site's R&D department and the date that the green light was given for the study to go ahead. This included a site initiation visit (SIV) and R&D confirmation of capability and

capacity, it did not include the time required for the HRA and REC approvals. At international sites, the timeframe included additional process including gaining ethical approval, review and signing of data sharing agreements, adaptation and translation of the study documents, translation/review of the LRRC-QoL questionnaire and the delivery of workstream I training to the study team.

Figure 9.3 illustrates the timelines for site setup at participating centres. The first four sites achieved setup prior to the peak of COVID-19 cases in January 2021 in the UK (see Figure 9.2), the longer setup times for the other UK sites may be a reflection of the impact of this peak in cases on R&D departments. The additional processes required to setup international sites are likely to account for these sites generally requiring longer for setup.

Figure 9.3: Chart illustrating site setup



***green shading indicates time in setup, blue shading indicates periods where study setup was on hold due to COVID-19, grey shading indicates sites which did not open to recruitment.**

9.7.1 Withdrawal of Sites Prior to Ethical Approval

Several difficulties were encountered during the drafting of the Data Sharing Agreement for use at the site in Mumbai, these included proposed intellectual property rights and jurisdiction of the agreement and governing law. The legal team based in Mumbai proposed utilisation of their own template for this purpose in the form of a Memorandum of Understanding (MoU). This was not deemed appropriate by the University of Leeds; MoUs are not considered legally binding and given that India does not have an adequacy decision in line with UK GDPR this was considered too high risk. A redrafted form of the Data Sharing Agreement was created with a view to satisfying the requirements of both parties; however, this was rejected by the Mumbai team and they withdrew from the study. As described above, the site in Dublin withdrew from the study due to difficulties gaining ethical approval.

9.8 Recruitment Strategy

9.8.1 UK Recruitment Strategy

The recruitment strategy for the UK was based on a Patient Identification Centre (PIC) model with a view to reducing the burden of research activities at a site level as much as possible. PIC sites are sites which identify potential participants for a study and direct them to a research centre to participate (345). PICs are not responsible for undertaking consent or any further trial specific procedures following referring the potential participant to the research centre. One of the benefits to a PIC model is that PIC sites can be setup rapidly by R&D departments through a sub-contract arrangement with the research centre that the PIC supports (345). A PIC model also reduces the responsibilities of research teams at a site level. However, in the case of the LRRC-QoL study, it was not

deemed possible to setup sites as PICs given that they would also be responsible for collecting clinical data for the study participants, this is considered a research activity and is therefore out with the restraints of a PIC site. Though the study sites are not technically PICs according to the criteria defined by the HRA, the PIC model inspired the approach to the study with the researcher co-ordinating quality of life follow-up centrally.

In this PIC-inspired approach, potential participants were approached by their clinical team at site and asked to provide consent to sharing their contact details with the researcher based at the University of Leeds. The researcher was then able to contact patients directly provided they consent to sharing their contact details by completing a short form. Completion of this form enabled teams based at sites to securely transfer potential participants' contact details to the researcher. Following this, the researcher would send a participation pack to the patient to complete and return via post, including a formal consent form, a demographics form, and the questionnaires. The researcher was then also able to contact potential participants to prompt them to return the questionnaires.

1.1.1 Flexibility in Study Delivery at International Sites

During the process of setting up international sites, several adaptations were introduced to the study design following discussion with the participating teams at these centres. The recruitment process and study delivery plan used in the UK were not necessarily suitable for centres in other parts of the world and a flexible approach was adopted given the cultural and logistical differences in the delivery of care for LRRC internationally. Prior to commencing setup at each participating centre, a videoconference SIV was arranged with the participating research team to discuss how to deliver the study most effectively, taking on board the expertise and experience of the clinical teams. Several key differences

were introduced to the study delivery at participating sites as a result of these discussions. Understandably, the majority of international sites felt that a PIC approach co-ordinated from the UK would not be feasible, given the lengths of time required for international postage and additional difficulties such as language barriers. It was therefore agreed that most international sites would co-ordinate recruitment locally.

Participating sites in English-speaking countries were offered the option of online participation, given that a REDCap platform and study website had been developed for this purpose in the UK. The possibility of online consent was also discussed with teams at non-English-speaking sites, the team from Denmark reported previous experience in delivering PROMs via an online platform and were therefore keen to include an option for patients to participate online (359). The teams based in the Netherlands also opted to pursue this approach as they felt their patients would engage well with online recruitment. Dutch and Danish versions of the REDCap forms were developed with input from these teams to make small adaptations to the language in the questionnaires and consent forms so that they were suitable for online use, for instance changing wording such as “please circle…” to “please select…” The online consent forms were hosted by the University of Leeds, participants would be explicitly consenting to sharing their personal details with the UK-based research team, which was acceptable from a GDPR perspective.

The participating teams in India and Pakistan shared their experience from conducting previous research; advising that sending out questionnaires via post was unlikely to yield a high return rate and would exclude patients with lower reading levels. Alternatively, they advised that a researcher complete the questionnaires for the participant by verbally posing the questions to them either in person during clinic appointments or via telephone.

This approach was therefore adopted for recruitment in South Asia and has been recognised as an acceptable and equivalent approach for administering PROMs such as the EORTC QLQ-C30 (291). At times co-ordinating a study with multiple centres approaching recruitment in slightly different ways could be challenging, particularly as the protocol needed to be updated following each change implemented, which may then require an amendment for sites open to recruitment. However, the flexibility in this approach and recognition of important cultural, clinical, and logistical differences were crucial to enabling sites in these countries to successfully participate in the study.

9.9 Summary

Setting up and co-ordinating a multi-centre, international research study has involved a very steep learning curve with multiple lessons and areas for improvement and personal growth. Many of the key learning points encountered related to the ethical and legal processes involved in setting up a research study; the HRA and REC approval processes were a completely new experience and with the benefit of hindsight, aspects of this process could have been conducted more efficiently. Potentially avoidable delays occurred at several points during the ethical approval application, such as in confirming the organisation that would act as sponsor for the study and when seeking advice from the REC regarding whether sites could be set up as PICs. Minor practical considerations, such as how to circulate the Local Information Pack to sites in an organised and efficient way, were also important learning points in optimising time-management and facilitating the process of site setup for R&D departments.

The process of developing contracts, the legislation, and the legal terminology involved, was also completely alien territory. Developing an understanding of this process was further complicated by a need to understand the ways in which international laws surrounding data processing and transfer interacted, in some instances in a contradictory fashion. Understanding these interactions was particularly difficult given the uncertainty and evolving changes prior to, during, and following Brexit. At a personal level, the day-to-day co-ordination, project oversight and leadership skills required in this role were very challenging. Occupying the role of a leader was arguably the most difficult challenge to overcome and had a pervasive impact on the project. Gaining experience, taking steps to build confidence and support from my supervisory team were essential to overcoming these difficulties.

Chapter 10 Strategies to Improve Recruitment to a Prospective, International, Multi-Centre Research Study in LRRC

10.1 Introduction

Recruiting patients with LRRC to clinical research studies is undeniably challenging. This has been demonstrated during the original development of the LRRC-QoL and was exacerbated by delays in site setup, a lack of engagement from the research team at one of the sites, and balancing against concurrent HrQoL studies at another site (108). The difficulty of recruiting patients with LRRC to research studies is arguably evident in the results of the systematic review described in chapter 2, with a predominance of single-centre retrospective cohort studies and combined cohorts of patients with advanced and recurrent disease. As highlighted in chapter 1, clinical outcome reporting in LRRC has been significantly advanced by collaboratives such as PelvEx through pooling international, multi-centre clinical data (35). However, these methods do not typically include a patient-perspective through reporting PROs. Additionally, this is not the optimal approach for establishing effectiveness of interventions or treatments, for which RCTs represent the gold standard. There are very few published RCTs in patients with LRRC to date, most likely due to the low incidence of LRRC combined with its advanced, heterogenous nature, complex treatment pathways, and a historic lack of focus on LRRC and its treatment.

The difficulties of recruiting patients with advanced or recurrent cancer more generally have been highlighted, with reasons for non-participation including limited prognosis, being too unwell to participate, experiencing severe distress or having other competing

priorities (302). Previous prospective studies in patients with advanced or recurrent rectal cancer have also illustrated the challenges of maintaining response rates during prospective QoL follow-up (98, 173, 360). Recruitment specifically to QoL studies in this group may be further impaired by a perception that QoL studies include topics that are considered sensitive or personal, such as sexual function (361).

Though recruiting patients with LRRC to clinical studies is known to be difficult, attempts to define and address recruitment challenges have been scarce. In a clinical trials setting, the QuinteT Recruitment Intervention (QRI) was developed to optimise recruitment to RCTs (362), and has demonstrated its effectiveness in identifying and addressing recruitment challenges across a number of trials (363). The QRI comprises two phases, phase 1 involves the identification of recruitment issues and phase 2 involves a process of designing and implementing strategies to address the issues identified in phase 1 (362). Though the study described in this thesis is not a clinical trial, the QRI is used as a framework for the approaches employed during the delivery of the study to drive improvements in recruitment rates. This chapter details the recruitment challenges identified during the study and the strategies which were successfully implemented; resulting in a cohort of more than 200 patients recruited for the external validation of the LRRC-QoL, which is described in chapter 6.

10.2 Methods

The LRRC-QoL study included two workstreams which contributed to the external validation of the LRRC-QoL measure, as detailed in chapter 6. These included workstream I: cross-cultural adaptation of the LRRC-QoL, and workstream II: a

prospective, longitudinal cohort study of HrQoL in LRRC. The overall recruitment target was 320 patients with an anticipated 10% attrition rate. Recruitment was intended to run for 12-months with a 12-month follow-up period.

The QRI approach was modified and applied to our prospective cohort study. Phase 1 of the QRI involves four central components, including, audio-recording of recruitment encounters, interviews with recruiters, mapping recruitment pathways, and reviewing trial documentation (362, 363). In the context of this study, phase 1 was modified to include a focus group with research nurses in place of qualitative interviews, monitoring of a central screening and recruitment log, and review of patient-facing study documents through patient and public involvement (PPI) work. We did not have the resources to enable audio-recording of recruitment encounters, and in addition, recruitment was undertaken remotely using telephone and postal-based methods. Formal interviews with recruiters were not pursued due to concerns regarding the potential burden on clinical and research teams given that the study commenced during the COVID-19 pandemic.

Phase 2 of the QRI involves the development and implementation of strategies to improve recruitment, through presenting the findings of phase 1 to the study management group, and agreeing a "*plan of action*" (362). These approaches were undertaken in the modified QRI applied in this study through presenting findings to the project supervisory team during monthly meetings and agreeing strategies to implement. Phases 1 and 2 ran in tandem to enable response to any additional challenges as they were identified. Screening and recruitment rates were monitored throughout the study duration to identify trends.

10.2.1 Phase 1: Understanding Recruitment Challenges

10.2.1.1 Analysis of Central Screening and Recruitment Logs

A screening and recruitment log was maintained centrally by the co-ordinating researcher (NM). This was facilitated through weekly communication with research teams to update the log for each site. The log was completed using the Screened, Eligible, Approached, Randomised (SEAR) framework (364), which was adapted to 'Recruited' for this observational study and enabled review of the patient recruitment pathway as per the QRI. The proportion of patients who were converted from eligible and approached to recruited was closely monitored. Variation in the numbers of patients screened at each site was anticipated given the rare nature of LRRC and differences in regional referral patterns, particularly internationally. Reasons for non-participation were recorded where possible, however this was not always achieved given that a significant proportion of patients were approached via post.

10.2.1.2 Research Team Focus Group Meeting

A research team focus group meeting via Microsoft Teams was arranged in September 2021, 10 months after the first site opened to recruitment. The aim of the meeting was to identify the reasons for patients not participating in workstream II and to develop strategies to improve recruitment. Research teams from all participating UK sites were invited to attend. International sites were not invited to attend as they were recruiting to workstream I at this time. Additionally, as described in chapter 9, recruitment strategies were tailored to participating international sites and their local processes, therefore sharing their experiences could have caused confusion in a meeting setting.

10.2.1.3 Patient and Public Involvement

PPI work was undertaken at two timepoints during the study and was conducted initially through individual interviews, followed by a second focus group meeting. Both the interviews and meeting were conducted via Microsoft Teams at a mutually convenient time. Patient representatives were identified via participating sites and social media posts on Facebook and Instagram cancer support pages by one of the patients identified. The first round of PPI work took place in October 2021 and aimed to gain a patient-perspective of the study processes and recruitment pathway, with particular focus on the patient-facing study materials. The second PPI meeting was held in May 2022, additional aims of this second meeting included reviewing reasons identified for non-participation and to identify strategies to improve recruitment to the study.

10.2.2 Phase 2: Implementing Changes

Changes to the study recruitment process and study documents were introduced at various timepoints and implemented through substantial and non-substantial amendments to the study ethical approvals. These changes were communicated to research teams via Microsoft Teams calls and via email. Regular newsletters were also circulated via both email and Twitter during the study to communicate updates.

10.3 Results

Research teams from three sites attended the focus group meeting in September 2021, namely St. Mark's Hospital, Harrow, UK, Addenbrooke's Hospital, Cambridge, UK, and Leicester Royal Infirmary, Leicester, UK. One of the sites had a high screening volume but lower conversion rates from eligible and approached to recruited. The other two sites

had lower screening volumes but higher conversion rates. There were five attendees, including, specialist nurses, research nurses, and research support staff. Three patients participated in the PPI work overall, one was identified from St. Mark's Hospital, one from Heartlands Hospital, Birmingham, UK, and one patient was identified via a social media post on a cancer support page. Two patients took part in the individual PPI interviews in October 2021 and two patients attended the PPI group meeting which took place on 30th May 2022.

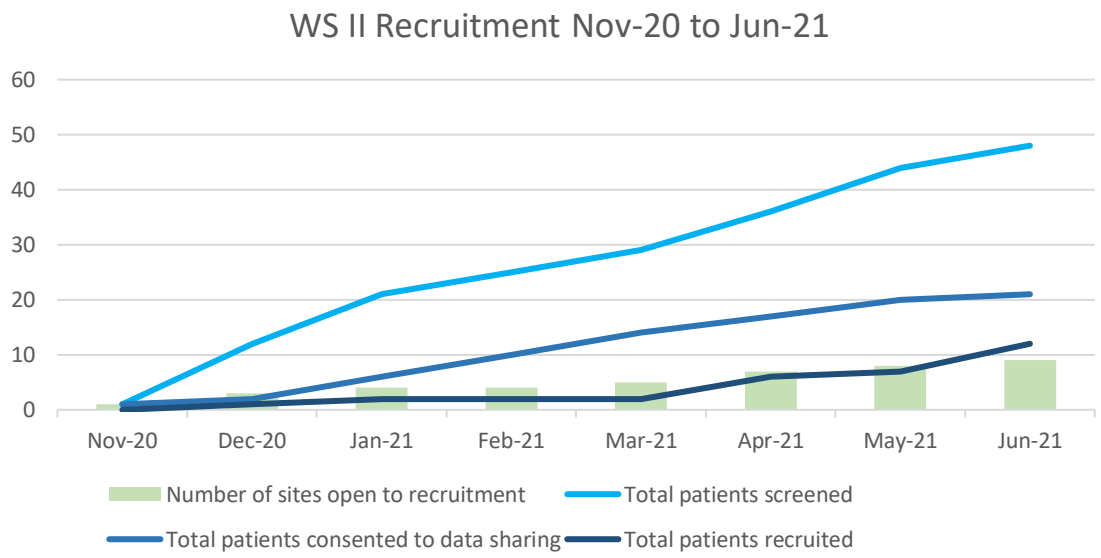
10.3.1 Phase 1: Identification of Recruitment Challenges and Strategies

10.3.1.1 Recruitment Challenges Identified

10.3.1.1.1 Structural and Organisational Issues

Review of the central screening and recruitment log within the first four months of the study indicated that the two-stage consent process utilised in the UK, described in chapter 9, risked missing the recruitment window between the time of diagnosis/referral to the specialist MDT and commencing treatment or undergoing surgery. The timeframe required to allow for mailing out and returning the consent to data sharing form followed by the participation pack was too long in several cases, meaning potential participants became ineligible to take part despite having been willing to do so. This may have been exacerbated by delays to the post due to increased pressure on the Royal Mail during the COVID-19 pandemic. Figure 10.1 demonstrates this effect on recruitment, with only a small proportion of patients who consented to sharing their personal data going on to be recruited into the study within the first 6 months of recruitment.

Figure 10.1: Workstream II recruitment November 2020 to June 2021



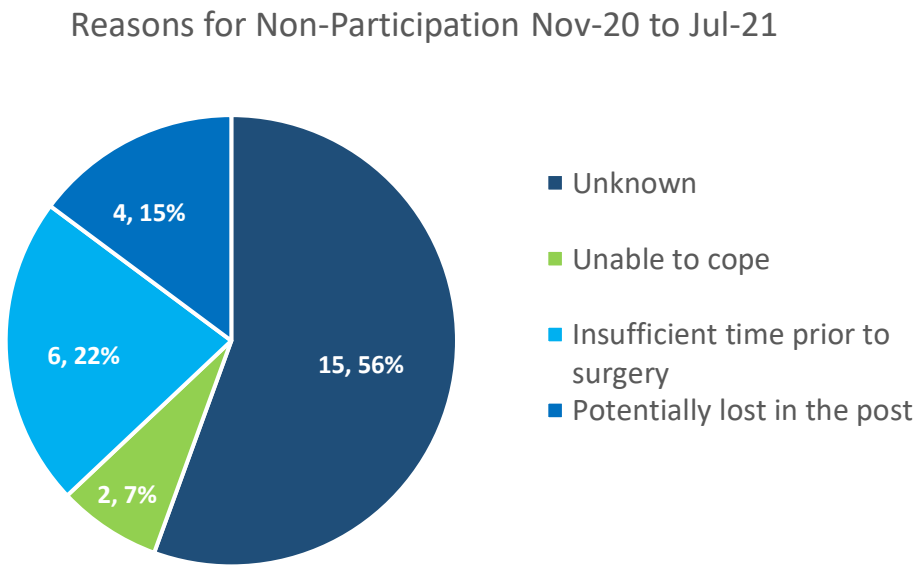
Measures to streamline the recruitment process were introduced in March 2021 and are detailed below in section 10.3.2.1. In August 2021, despite the introduction of these measures, the rate of patients recruited from those approached remained at 20-25%. Though recruitment to QoL studies in patients with advanced or recurrent colorectal cancer tends to be lower than in other patient groups, this was still lower than anticipated. Compared with the 38.8% reported in the psychometric analysis of the LRRC-QoL in the UK (108) and with other studies regarding QoL in this disease group, reporting recruitment rates of around 40% (115, 116). Recognition of the consistently low conversion rate prompted reflection and steps were undertaken to identify the reasons for non-participation through PPI work and Research Team Focus Group Meetings.

10.3.1.1.2 Barriers to Participation

In March 2021, review of the screening and recruitment log, combined with discussions with research teams, identified several reasons for non-participation. Forty-eight patients

had been screened and met the eligibility criteria at this timepoint, with 21 having consented to data-sharing, of which 12 were recruited. Regarding the 27 patients who did not consent to data-sharing, reasons for non-participation included the limited timeframe for recruitment being exceeded as described above (n=6, 22%), other reasons included patients reporting that they did not feel able to cope with participating in a research study following being diagnosed with recurrence and preparing to commence treatment and/or undergo major surgery (n=2, 7%). Four (15%) patients reported having returned the participation pack, however these were never received by the researcher, this may have been due to issues with the postal service, though in the majority of cases the reason for non-participation was unknown (n=15, 56%) (see Figure 10.2).

Figure 10.2: Reasons for non-participation in Workstream II November 2020 to July 2021



The research team focus group meeting confirmed the issues identified, including patients being "*overwhelmed by the amount of information they receive around the time of diagnosis and whilst preparing for surgery*", some patients also found the questionnaires

upsetting. Additionally, several patients who had been followed-up by telephone reported receiving the pack in the post but had either misplaced or forgotten about it. Other patients reported not having time to complete the questionnaires. In terms of the challenges and barriers to recruitment, research teams reported that it was "*challenging to get patients to invest in the study when they have not yet met the clinical team*", particularly in cases where patients had been referred from geographically distant locations and were unable to attend clinic face-to-face due to the distance and the COVID-19 pandemic. Other sites reported difficulty given the "*rare group of patients*" of interest, identifying small numbers of eligible patients during the screening process. All attendees agreed with a plan to undertake PPI work to improve the study patient information leaflets (PILs) and agreed to try help identify potential PPI participants.

10.3.1.2 Strategies Identified

10.3.1.2.1 Strategies Related to the Recruitment Pathway

During the process of reviewing the screening and recruitment log, in addition to discussing site setup with international sites, including those in the USA, the Netherlands, and Denmark, the potential to recruit patients online was highlighted. Online consent and PROMs completion enables remote recruitment and follow-up within research studies which can offer significant benefits, such as removing the need for face-to-face contact for recruitment, particularly important during the COVID-19 pandemic, and can be more cost-effective than postal based methods (365).

During the research team focus group meeting, several strategies were identified which sites felt had been successful during the opening months of the study. One research team reported that "*approaching patients face-to-face in clinic has generally been successful*"

and that follow-up telephone contact from the research teams based at site was helpful in prompting patients to complete and return the forms. All teams participating in the meeting stated that weekly contact from the central research team was helpful in prompting them to screen and approach eligible patients.

In relation to potential changes, one of the research teams suggested "*sending out less information to patients – sending out a letter and card with the website details on it and see if this helps improve recruitment*" in lieu of the full paper-based participation pack, as they felt the amount of information was potentially off-putting for patients. Another strategy proposed was for the clinical team to consent patients verbally to sharing their personal contact details with the research team, meaning that the research team would be able to contact patients directly in relation to the study. The process of undertaking written consent to contact had previously proved slow, resulting in eligible patients missing the window for participation prior to commencing treatment. Verbal consent via telephone presented a potentially more time-efficient process for patients not being seen face-to-face in clinic. This approach had previously been considered in the initial study design and was discussed informally with experienced trial managers at the CTRU and more formally with the University Sponsor and through seeking advice from a REC representative. This approach was ultimately not pursued in the initial ethical application due to concerns that it would not be approved by the REC and may require an additional Confidentiality Advisory Group (CAG) approval.

Finally, a proposal to give patients the option to complete the PROMs via telephone with the researcher was discussed. Sites felt that some patients may like this approach to

participation and that they would support its inclusion as an alternative option in addition to the traditional postal-based approach and online recruitment.

10.3.1.2.2 Suggested Changes to the Patient Information Leaflets

The PILs were reviewed during the PPI interviews held in October 2021. Regarding their general appearance, both patients interviewed felt they contained too much information and should be shortened to "*the headlines*" or "*bullet points*". During the second interview, the patient suggested using "*text boxes across the page to help draw attention*" as an alternative to the columnar structure which had been used. In terms of the front page, the first patient interviewed suggested adding the study aims to the front page of all the PILs and both contributors felt that diagrams would be helpful to explain the study. In terms of the level of language and terminology used, both patients felt this was acceptable, easy to understand throughout, and in no way offensive or upsetting.

Both patients felt the overall explanation of workstream II was adequate, but more information should be provided in relation to how the study results would be used to affect care. One of the patients also suggested adding icons or images to the background information sections to help explain the study in a more engaging manner. They also advised moving the phrase "*there are no personal benefits to taking part in the study*", to the end of the "*What are the benefits of taking part?*" section as they felt it would be better to begin with a more positive statement regarding the study results could be used to guide and improve patient care in the future.

The information related to the management of data was felt to be excessive, though they recognised it was necessary to provide this information, both patients were in favour of

its inclusion as an additional supplement or in smaller print at the end of the leaflet. The second patient interviewed also advised changing the title of this section to "*My data, how will it be used*?". Both patients also felt that it would be better to remove "parts A and B", simplifying this to explain that patients could choose to opt in to completing an additional questionnaire at 10-14 days.

10.3.1.2.3 Addressing Barriers to Recruitment

These reasons for non-participation previously identified were discussed in turn during the PPI group meeting in May 2022.

> *"Finding it "too much" mentally or "overwhelming" around the time of diagnosis with LRRC."*

The PPI group discussed this issue and were unsure that there was anything that could be done to avoid this, they suggested highlighting the intended benefits of the study in improving patient care and enabling use of the questionnaire in future research. They felt that the "*possibility of improving care for patients in the future*" would be a strong motivating factor to take part in the research.

> *Finding the questionnaires upsetting.*

The PPI group had conflicting views, one of the patients could empathise with this issue as they felt they may also find the process of reflecting on their experiences upsetting or traumatic, particularly now that they have completed their treatment. However, the member of the PPI group who was participating in the study felt strongly that the questionnaires were not upsetting.

Not having enough time to take part due to preparing for surgery or receiving treatment such as radiotherapy.

Both members of the PPI group could also empathise with this reason for non-participation and again suggested highlighting the intended benefits of the study to encourage patients to take part.

Receiving the participation pack but forgetting to complete it.

Both members of the PPI group supported the suggestion to send out reminders in the form of sending another pack and calling patients via phone, they did not feel this would be too intrusive, provided it was done sensitively.

10.3.1.2.4 Study Newsletters and Collaborative Networks

Other multi-centre studies which were open to recruitment during the same period had demonstrated the success of using newsletters circulated via Twitter to generate interest and promote recruitment (366, 367). This approach was therefore employed during the delivery of the LRRC-QoL study. The initial proposal for the project consisted of a plan to translate the LRRC-QoL measure into four languages, Danish, French, Dutch and Swedish and to run the study at six sites in the UK, two in Australia and one in Dublin. This network of collaborators was established during the original development of the LRRC-QoL questionnaire (108). The network was extended during this project through partnering with existing exenterative surgical networks, including the UK Pelvic Exenteration Network and the PelvEx international collaborative, both networks shared details of the study with their members via email.

10.3.2 Phase 2: Changes Implemented

10.3.2.1 Recruitment Pathway

10.3.2.1.1 Removal of Two-Stage Recruitment Process and Introduction of Online Consent

A substantial amendment was submitted and approved in March 2021 in response to the challenges associated with the two-stage consent process identified through scrutinising the screening and recruitment log. The amendment consisted of a change to the recruitment process to enable participating sites to send participation packs to patients with a pre-paid envelope to return them directly to the researcher based at the University of Leeds. This eliminated the two-stage consent process. The amendment also included approval to undertake online consent and completion of the demographics form and questionnaires via REDCap, a study website was created to enable potential participants to view the PILs online. The new recruitment approach was implemented from March 2021 and the website and the English-language REDCap went live in June 2021 (368). Dutch and Danish online consent and PROMs completion were later introduced for workstream II following cross-cultural adaptation in these languages.

10.3.2.1.2 Verbal Consent to Contact and Participation via Telephone

Following the first research team focus group meeting, the following changes were agreed for implementation:

- Sending out less information to patients in the form of an introductory letter and card with link to online information,
- Verbal consent to sharing contact details with the research team,
- Additional option to complete PROMs via telephone.

The submission of an amendment to the REC was required to implement these changes and the inclusion of changes to the procedures undertaken by participants constituted a substantial amendment, necessitating formal REC review. Given the previous concerns regarding undertaking verbal telephone consent to sharing personal contact details and consent to the study overall, the REC that approved the study was contacted for guidance regarding whether this approach would be tenable from an ethical standpoint. The REC advised submitting a substantial amendment for further consideration. Following sponsor approval, an amendment to this effect was submitted at the beginning of October 2021. The option to complete the PROMs via telephone was also submitted in a substantial amendment in October 2021, following advice by the sponsor at the University of Leeds to clarify that consent forms would be signed by the researcher when verbal consent was given via telephone and then posted to the participant to review, with the opportunity to raise any concerns.

The PPI work was still underway at the time of submitting this amendment, therefore no changes to the PILs were proposed with the intention to submit a further amendment shortly after with the updated PILs. For this reason, the amendment submitted in October 2021 was initially rejected due to not including the updated PILs, it was resubmitted with the updated PILs on the 14th of December 2021 and approved on the 21st of December (see Figure 10.3).

10.3.2.2 Patient Information Leaflets

The following changes to the PILs were implemented following the PPI interviews:

- Formatting changed from columnar layout to text boxes across the page for all PILs,
- Study aims added to the front page of all PILs,
- Information added to all PILs detailing how the study results would be used to affect patient care,
- The phrase “there are no personal benefits to taking part in the study” was moved to the end of the “What are the benefits of taking part?” section for all PILs,
- Information regarding data management moved to a supplement at the end of each PIL titled, “My data, how will it be used?”,
- Diagram added to summarise workstream II,
- The inclusion of “parts A and B” removed from workstream II and changed to text explaining patients have the option to complete an additional questionnaire at 10-14 days.

These changes were implemented to the PILs and circulated to the PPI members for further discussion and their final approval. As described, they were submitted to the REC and approved in December 2021 (see Figure 10.3).

10.3.2.3 Study Newsletter and Communication with Sites

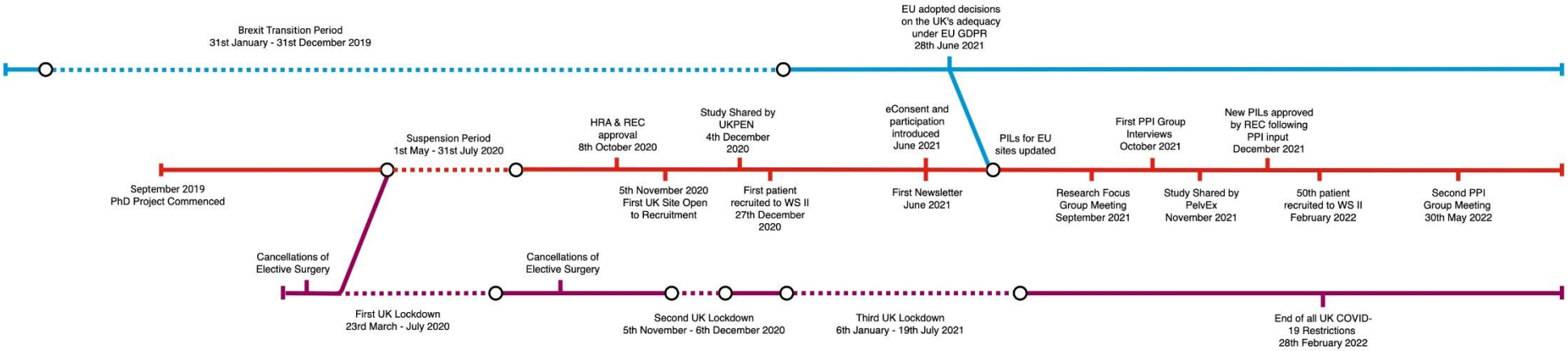
The first newsletter for the LRRC-QoL study was circulated in June 2021, detailing progress with ethical approvals, translation of the LRRC-QoL questionnaire and site setup progress in the UK (369). This was followed by subsequent iterations detailing recruitment updates and a leader board listing the top three recruiting sites overall. At some sites, levels of engagement with the study fluctuated over its course. Regular

communication via email in addition to circulating the newsletters was utilised to try and engage collaborators as much as possible.

The recruitment strategies which had been highlighted in the research team focus group meeting were circulated in the Autumn 2021 newsletter, these included:

- approaching patients face-to-face where possible,
- re-contacting potential participants via telephone and second mail-out at 2 weeks following initial contact if the central research team had not received the study pack,
- Consenting patients to data sharing to enable the central research team to contact them directly.

Figure 10.3: Timeline of study delivery and strategies to improve recruitment

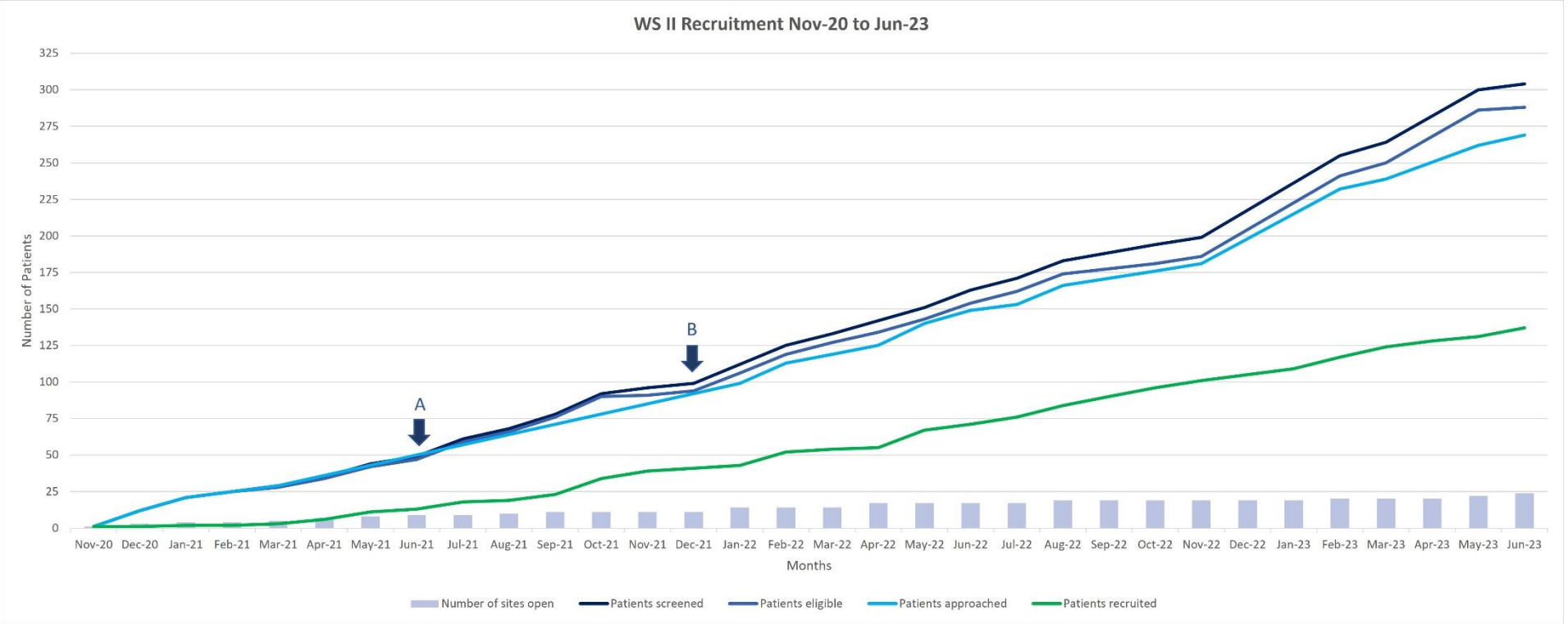


10.4 Impact on the Study and Recruitment Rates

10.4.1 Overall Recruitment

Workstream II was open to recruitment from November 2020 to June 2023 and recruitment rates are illustrated in Figure 10.4. Overall, 304 patients were screened for the study, of which 288 were eligible and 269 approached. Reasons for not approaching eligible patients included patients experiencing high levels of distress during consultations resulting in the clinical team feeling it was not appropriate to approach, and not being able to contact patients prior to them commencing treatment, particularly those not receiving treatment at the specialist centre they had been referred to. In total, 137 patients were recruited to the study up until July 2023, representing 50.9% of those approached. A recruitment conversion rate of 50% was first achieved in July 2022 and maintained at this level or higher for the remainder of the study. There are several factors which are likely to have contributed, including the addition of two new sites and conversion of four sites from workstream I to II in early 2022. The timing also reflects the combined effect of the changes implemented to the study including online consent from June 2021, and the changes to recruitment process and PILs introduced in December 2021.

Figure 10.4: Overall recruitment by month



***Timepoint A indicates the introduction of online consent and participation, timepoint B indicates the introduction of the revised PILs and verbal consent to contact.**

10.4.2 Online Recruitment

From the introduction of eConsent in June 2021, 64 participants were recruited to the study via REDCap from the UK, the Netherlands, New Zealand, and Canada. Representing 31.4% of recruitment to workstreams I and II overall. During the delivery of the study, online consent and participation offered several benefits. The ability to complete PROMs online with direct transfer to the central research team was both time-efficient and cost-effective; at international sites in the Netherlands, New Zealand, and Canada, this eliminated the need for the local team to collect and transfer PROMs data. Patients who chose to participate online cited reasons including this approach being quicker, easier, and more environmentally friendly. However, online recruitment was not implemented for all sites and languages, discussions were held with participating teams at each international site prior to setup to select the best approach to recruitment. Many sites felt that online recruitment would not be well received or feasible for their local cohort of patients. Additionally, it would have been challenging from an implementation perspective to build REDCap surveys in every language. Other issues encountered included website downtime which occasionally interfered with automated follow-up emails.

10.4.3 Research Teams

During the focus group meeting and later at the 2022 PelvEx meeting in Amsterdam, collaborators reported that the Newsletters and weekly emails were helpful in reminding them to recruit to the study. The use of social media, namely Twitter, also helped to engage collaborators, with research teams competing to be the study's top recruiting site. Partnering with the UKPEN and PelvEx collaborative networks generated interest, including sites in India, Canada, Brazil, and Russia, providing an increase in sites from

the initial thirteen sites to thirty-seven sites by June 2022. The study being charity-funded and therefore eligible for the National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN) portfolio, also led to interest from new sites in the UK.

10.5 Discussion

Overall, the interventions described in this chapter had a significant positive impact on recruitment to the study, with the conversion rate improving from the initial 20-25% to 50% by Summer 2022 and remaining at this rate or higher until completion. Though a conversion rate of 50% may seem relatively low, it is higher than those previously reported in PROMs studies of patients with advanced cancer (108, 115, 116, 302) and represents a significant achievement in this setting. The improvement in this rate from July 2022 suggests it occurred as a direct result of the recruitment strategies introduced in the preceding months, including changes to the recruitment process, such as verbal consent to contact, and utilising PPI input to update the PILs. The results also demonstrate that although recruiting patients with LRRC to research studies presents numerous challenges, strategies have now been identified which can be successfully applied to address this.

Several barriers to recruitment specifically related to LRRC were identified, these included patients feeling distressed or overwhelmed around the time of diagnosis. These feelings are similar to those previously described in patients receiving palliative treatment (302), demonstrating the advanced nature of LRRC and its psychological impact. Where patients were referred to specialist centres from other sites, a lack of previous contact with the clinical team at the specialist centre could act as a barrier to recruitment.

Specialist centres were selected as sites for the study with a view to maximising recruitment, however this brought additional challenges which need to be considered within the development of recruitment pathways. These include the timing of approach for consent; allowing sufficient time for the clinical team to build rapport with the patient, whilst leaving enough time for the patient to participate before commencing treatment. From a study design perspective, the initial study recruitment process was found to be overly complicated and convoluted, causing the recruitment window to be missed.

A number of strategies were identified which successfully addressed these issues. The two-stage recruitment pathway was refined, resulting in a more streamlined approach. Utilising verbal consent to contact enabled the recruitment encounter to be undertaken remotely by the central research team. This was effective, particularly as the central team were likely to have more time to devote to this process than the research teams at sites. Recruitment rates also improved in response to the introduction of multiple options for participation, including traditional paper-based methods, online, and via telephone. Additionally, the study newsletters, regular email communication with sites, and involvement of collaborative networks, were easy to implement and had a significant impact on the study. In relation to patients feeling overwhelmed by the volume of information received both in relation to potential treatments and the LRRC-QoL study, this was addressed by refining the PILs with input from PPI representatives. It was not possible to address all the recruitment issues identified, specifically patients declining to participate due to feeling distressed around the time of diagnosis with LRRC. Prospective HrQoL studies offer greater value if baseline measures are included, enabling comparison over time, necessitating a recruitment process close to the time of diagnosis, despite this being a potentially distressing time for patients. Approaching recruitment sensitively is essential under these circumstances and was implemented across this study.

The last decade has seen increasing focus on improving the delivery of clinical studies and particularly RCTs, through initiatives such as Trial Forge which was established in 2014 to improve randomised trial efficiency and quality. Their approach focuses on 'marginal gains'; introducing small changes in trial processes with a view to improving the overall trial system (370). This approach was also adopted in the LRRC-QoL study, through implementing a range of strategies in short succession. One of the central focuses of Trial Forge is to increase the body of evidence available to teams developing RCTs regarding design, conduct, and reporting (371). Studies within a Trial (SWATs) are an important tool in building this evidence base (371), and have previously demonstrated the value of interventions related to recruitment and strategies to improve response rates to follow-up questionnaires. Existing evidence produced by SWATs was used to inform some of the decisions undertaken during the delivery of the LRRC-QoL study. In relation to follow-up rates, the use of personalised text message prompts and financial incentives (372), have both been reported to have a positive impact. It was not possible to introduce financial incentives within the current study from a funding perspective, however personalised follow-up letters and/or emails were employed. Though SWATs are a valuable instrument in identifying strategies to improve the delivery of clinical trials, they are unlikely to be feasible in rare disease settings, such as LRRC. The numbers of patients required for a SWAT to deliver meaningful results is likely to be impossible to achieve in this context. The results reported in this chapter are a valuable contribution to the evidence regarding challenges and strategies to improve recruitment in LRRC and should be considered in the development of future clinical studies.

This work represents one of the first studies to report a detailed exploration of recruitment difficulties in the context of LRRC. The utilisation of the QRI to inform this work is a significant strength and led to the identification of effective strategies to improve recruitment in this challenging setting. Given the increasing focus on improving outcomes in patients with advanced and recurrent colorectal cancer, evidenced through initiatives including IMPACT, UKPEN and PelvEx, identification of these strategies could be invaluable to researchers planning future studies. In relation to the methods applied in this study, it is possible that the central screening and recruitment log was not completely accurate. The log was updated in line with communications between the co-ordinating researcher (NM) and research teams at sites, it is possible that patients were screened peripherally without the central team's knowledge. Regular communications were maintained to ensure it was as accurate as possible. Regarding PPI, the small numbers of patients participating in this work represents a limitation, this was the case due to difficulties identifying patients with a history of LRRC who were able to participate. Additionally, the PPI work and research team focus group meeting were exclusively conducted with English sites and patients, meaning their outcomes are not necessarily generalisable. This decision was undertaken due to the tailored recruitment approaches implemented across international sites, meaning holding a meeting for all research teams may have caused confusion due to the range of approaches applied. From a practical standpoint, conducting international PPI work would have been challenging due to language barriers. One of the key limitations of this work was that the study did not implement the QRI in its entirety utilising qualitative methodology. Interviews with recruiters and audio-recordings of recruitment encounters could have highlighted additional issues, though were not necessarily the most appropriate methods for this study given the recruitment approaches applied. Future trials in LRRC could consider

incorporating the QRI with a view to confirming and building upon the evidence reported in this chapter.

The evidence and experiences gained during the delivery of the studies described in this thesis offer several key messages which should be used to inform the design and delivery of future studies in LRRC. Firstly, undertaking PPI work regarding study delivery processes, and particularly in relation to developing PILs and recruitment strategies, had a resounding positive impact on the study overall. The initial study design was informed by the original LRRC-QoL development study and the recruitment challenges experienced during its delivery (108). PPI was undertaken and reported less frequently, particularly in surgical research studies around this time (373, 374). Whereas many funders now stipulate that PPI work is undertaken during the development of research proposals, including NIHR (375). Recent developments such as the introduction of the UK Standards for Public Involvement (UKSPI) (376), have also helped to improve the delivery of PPI. This includes the adoption of virtual methods during the COVID-19 pandemic (377), as was the case in this study. In hindsight, PPI should have been conducted earlier during the study design process and prior to the initial ethical approval. This would have saved time and effort in gaining approval for a substantial amendment via the REC and then at each participating site, in addition to averting the effort and resources required to circulate the new PILs. Moving forwards, high quality PPI work should be considered a routine aspect of the design and implementation process for all clinical studies in LRRC.

Previous work examining PILs have shown the importance of ensuring they are comprehensible, using plain language, and have an attractive layout and structure, with

diagrams to support textual information (378). In addition to high levels of PILs which contain language considered too complex to be accessible to patients (379). The suggestions made by the LRRC-QoL PPI group echo these findings as many of the changes to the PILs related to layout and structure. The PPI group were emphatic in their opinion that the PILs were too long overall, particularly the section regarding information governance and data protection. Researchers are required to include this information from a legal perspective and for the study documents to receive ethical approval, particularly following the introduction of the General Data Protection Regulation (GDPR) in 2016. The inclusion of information regarding information governance in PILs therefore applies to all research studies collecting personal and clinical data in some capacity and is not unique to this study. Previous PPI work undertaken prior to the introduction of GDPR has shown that patients prefer to access more brief materials and that these can be adequate to provide informed consent (380). Perhaps future work with stakeholders and input from PPI groups could be undertaken to review balancing the volume of information related to information governance which is required to be included by law against the volume of information patients prefer and is adequate to provide informed consent. Additionally, there are alternative methods for conveying study information, including multimedia informational videos and illustrations or diagrams. The addition of diagrams to the PILs in the LRRC-QoL study is likely to have contributed to the improvement in recruitment rates following their introduction. The use of informational videos has been examined through SWATs, which reported that they may help patients to better understand the information being communicated, however have not demonstrated a recruitment benefit (381, 382). Funding was not available to enable the creation of informational videos for the LRRC-QoL study, particularly given the number of languages required. However, this could be explored in future studies.

Developing an understanding of clinical pathways at a site level, particularly in complex disease settings such as LRRC, is imperative to developing streamlined recruitment pathways which will complement sites' existing processes. The effectiveness of this approach in relation to improving recruitment has previously been demonstrated in the context of COVID-19 (383) and is evident in the response to the changes introduced to the LRRC-QoL study recruitment pathway. The two-stage consent process initially implemented had a negative impact on the study. Introducing a more streamlined process, in addition to verbal consent to contact, contributed significantly to the improvement in conversion rate. On reflection, undertaking verbal consent for the research team to contact potential participants could have been included in the initial REC application. It is difficult to know for certain if this would have been approved at that time, as the evidence provided in the amendment application regarding the difficulties experienced in the first months of recruitment may have affected the committee's decision. The choice not to include this in the initial application was made in the context of the advice received at the time and was made with a view to obtaining ethical approval efficiently and without delays. Future studies should consider this approach from the offset given its proven efficacy and acceptability.

During the LRRC-QoL study, follow-up was co-ordinated centrally for the majority of English-speaking sites, in addition to sites in the Netherlands and Denmark, where patients had the option to participate online via REDCap. This approach was primarily implemented with a view to reducing workload for participating research teams and positively contributed to clinician buy-in, particularly during the pandemic, with reduced availability of research staff support. However, this does require a central researcher with capacity to undertake and closely monitor follow-up, additionally, some patients may be more likely to respond to contact from their local team. Though prospective HrQoL

studies reported from RPAH, Sydney, have achieved comparable follow-up rates of around 70% at 6-months (32). Considering its strengths and limitations, central co-ordination had an overall positive impact on follow-up retention rates and in gaining feasibility decisions from sites given the reduced burden of follow-up. Where feasible, it should be considered for all future studies involving prospective HrQoL assessments in LRRC.

Additionally, maintaining regular communication with participating teams and circulating periodic Newsletters via email and Twitter were easy to implement and demonstrated their significant value within the context of the studies described in this thesis. Communication involved weekly emails following MDT meetings to prompt identification of potential participants and email reminders to conduct follow-up for sites co-ordinating this locally. Harnessing the benefits of social media to share newsletters detailing study progress helped engage collaborators and the inclusion of a leader board helped foster a degree of healthy competition between sites (366, 367). In terms of studies recruiting in the UK, where eligible, utilising the resources available via the NIHR CRN portfolio provided benefits in the form of additional support from research teams and new potential sites becoming aware of the study via the portfolio (384). Undoubtedly, these interventions should be adopted across all studies in patients with LRRC given that all can be implemented with minimal resources and a potentially significant impact.

Another strategy which should also be implemented routinely in future studies reporting HrQoL in LRRC is offering a variety of methods for completing the LRRC-QoL, including face-to-face, postal, telephone, and online. The confirmed equivalence across different modes of PROMs administration supports this flexible approach (291).

Furthermore, the ePROM version of the LRRC-QoL was developed in keeping with both EORTC and ISPOR guidance (385, 386). This involved implementing very minor modifications to instructions regarding how to complete the ePROM, followed by cognitive interview and usability testing, as described in chapter 5 of this thesis. Undertaking discussions with sites and offering flexibility in the approach to modes of recruitment and follow-up had a significant positive impact on the study. The importance and necessity of flexibility in the approach to collecting PROMs data has previously been identified by other research groups working in a similar setting (387). In the context of the LRRC-QoL study, this facilitated recruitment by ensuring that the approach implemented was appropriate to the local population and participating clinical team. Though it may be more difficult to introduce flexibility within RCT settings compared with observational studies, offering different methods of PROM completion should still be considered.

Additional recruitment strategies could be identified through collaboration between researchers and PPI groups working within other rare disease areas. Collaboratives such as UK PEN (48), and PelvEx (34-42, 44, 47, 388-390) have demonstrated the value of collaboration within the field of research related to exenterative surgery; the ability to partner with these existing collaborative networks and draw upon their resources was incredibly beneficial in rapidly identifying new sites for the LRRC-QoL study. Collaboration more broadly through initiatives such as the European Reference Networks (ERNs) for rare diseases and complex conditions, and the International Rare Diseases Research Consortium (IRDiRC) (391), may also provide learning opportunities and resources to help inform and guide recruitment strategies from researchers working in rare diseases across a range of medical specialties.

10.6 Conclusion

Conducting an international, multi-centre prospective cohort study of HrQoL in a relatively rare disease involved many challenges, particularly in relation to recruitment. The recruitment challenges and strategies identified during the delivery of this study provide several recommendations for future work in this field. These include undertaking PPI work during study development, particularly to advise regarding PILs and recruitment strategies, and ensuring flexibility in recruitment and study delivery approaches, particularly at international sites. Other recommendations include partnering with existing collaborative networks where possible and maintaining regular communication with sites, including regular study newsletters. Future collaborative work could be undertaken to identify additional recruitment strategies which are effective in rare disease settings, such as LRRC.

Chapter 11 Discussion

11.1 Introduction

There are three central components of this thesis. The first relates to the quality of reporting of PROMs in LRRC, which is explored through a systematic review (chapter 2) and a comparison of HrQoL outcomes in patients with PRC and LRRC utilising registry data (chapter 3). Secondly, the ongoing development of the LRRC-QoL measure is described through the psychometric analysis to validate the measure for use in the UK and Australia (chapter 4), cross-cultural adaptation to enable its use in a number of languages and cultures (chapter 5), culminating in the external validation of the measure in an international cohort (chapter 6). In addition to longitudinal, prospective HrQoL assessment from baseline diagnosis up to 6-months utilising the LRRC-QoL (chapter 7). Finally, the long-term survivorship issues experienced by patients with LRRC are identified and described in chapter 8.

11.2 Summary of the Findings

11.2.1 The Quality of Reporting PROMs in LRRC

The evidence regarding HrQoL in LRRC has been examined extensively (97, 103, 104), with the lack of disease-specific PROMs for use in LRRC highlighted in 2015 (104). Nearly a decade later, this limitation remains, with no studies utilising LRRC-specific PROMs identified in the systematic review reported in chapter 2 of this thesis. The review highlights the current issues in reporting PROMs in LRRC from a methodological standpoint. Crucially, it identifies the ongoing lack of validated PROMs for use in LRRC,

given that none of the measures currently being used have demonstrated content validity in patients with LRRC. Other important findings include a lack of consistency in the way PROMs are reported in LRRC, particularly in defining the PRO of interest and in handling missing PROM data. Chapter 3 conveys the potential benefits of utilising registry data to compare HrQoL outcomes between patients with PRC and LRRC. The study described in this chapter confirms that patients with LRRC experience worse overall outcomes as assessed using the FACT-C CCS and demonstrates the ability of this measure to distinguish between these patient groups. The findings described in these chapters have important implications relating to future HrQoL reporting in patients with LRRC.

11.2.2 The LRRC-QoL Measure

The psychometric analysis of the LRRC-QoL described in chapter 4 validates this measure for use in patients with LRRC up to 2 years post diagnosis or surgery in the UK and Australia. This analysis has now been published (392), enabling its use in both clinical and academic settings as the first disease-specific measure of HrQoL in LRRC. The cross-cultural adaptation of the LRRC-QoL (chapter 5) resulted in conceptually equivalent versions for use in 10 languages and 14 countries, demonstrating the international relevance and acceptability of this measure across five continents. The international external validation analysis described in chapter 6 confirms the psychometric properties of the measure, building on the analysis described in chapter 4 in providing strong evidence for convergent and known groups validity. Additionally, establishing the LRRC-QoL's responsiveness to clinical change, which further enabled the prospective, longitudinal cohort study detailed in chapter 7. This study demonstrated that overall HrQoL deteriorates from baseline at 3- and 6-months in patients receiving

treatment with curative intent. Contrastingly, overall HrQoL improves over this time period in patients receiving treatment with palliative intent.

11.2.3 Survivorship in LRRC

The mixed-methods study described in chapter 8 identified the issues relevant to longer-term survivors of LRRC. Eight major survivorship themes and one theme related to adjusting to life following diagnosis and treatment, were identified. The survivorship themes related to experiences of long-term follow-up care, unmet needs, long-term physical effects of LRRC and treatment, issues related to stomas, urostomies, or urinary devices, psychological impact, impact on sexual function, and on daily life, and feelings surrounding life now and the future. These findings were somewhat unanticipated given their similarities to the issues previously described in patients less than 2 years from diagnosis or treatment (106, 143). This contrasts the evidence reported in primary malignancies where patients typically report different experiences to those who have more recently undergone treatment (119), and has important implications for survivorship care and the utilisation of the LRRC-QoL to report long-term HrQoL in LRRC.

11.2.4 Recruiting to Studies in LRRC

The process of setting up the studies described in this thesis and recruiting patients with LRRC was challenging. The implementation of a modified QRI identified several effective strategies to improve recruitment rates and minimise follow-up drop-off, as detailed in chapter 10. The combination of strategies employed contributed to improving the recruitment rates to above 50%. The process of implementing these strategies highlighted several approaches to optimise study design in this complex disease setting

with important learning points for future studies in LRRC and potential applications in other rare disease settings.

11.3 Strengths and Limitations

11.3.1 Evaluating the Quality of Reporting PROMs in LRRC

The methodological approach to the systematic review described in chapter 2 provides novel insights relating to the quality of PROMs reporting in LRRC. Particularly through utilising the COSMIN risk of bias checklist to interrogate the psychometric properties of the PROMs identified. Though the lack of disease-specific PROMs for use in LRRC has previously been reported (104), establishing that none of the PROMs currently in use demonstrate content validity in patients with LRRC represents a valuable addition to the literature. These findings also raise important questions regarding the ongoing use of these PROMs in patients with LRRC. Additionally, they provide further evidence to support the LRRC-QoL as the only disease-specific measure validated for use in LRRC.

The methodological focus was a significant strength of the review, however, assessment of reporting standards for PRO data was limited by the lack of an appropriate checklist or evaluation tool to appraise the quality of PRO-reporting in observational studies. Consequently, the CONSORT-PRO extension was adapted for this purpose. This has important implications given that it was developed as a reporting guideline (152), and not as a tool to appraise the quality of evidence, though it has frequently been utilised for this purpose (220). Modified versions of ten of the 14 items were included, meaning these results may not be comparable with those reported in other studies utilising CONSORT-PRO to appraise reporting standards.

Following this appraisal of the quality of PROMs reporting in LRRC, HrQoL reporting in LRRC was further explored in a registry-based study comparing PROs in patients with PRC and LRRC, as described in chapter 3. The demonstration that UK colorectal cancer registry data can be used to compare HrQoL outcomes between patients with LRRC and PRC has significant implications regarding the reporting of PROs in LRRC. Accessing national-level data via CORECT-R included a comprehensive application process involving PPI to ensure that the proposal was feasible and had a clear potential benefit to both patients and the public (393), which underlines the value of this work. However, the study and its utilisation of registry data was accompanied by several limitations, as previously highlighted in chapter 3. These included the significant heterogeneity in the two datasets which were included in the analysis, meaning many of the clinical outcomes were not directly comparable. The PROM data included in CORECT-R is not currently fully cross-linked, which also limited the ability to compare clinical outcomes between patients with PRC and LRRC. A major limitation was the inability to compare scores for the full FACT-C measure due to only the FACT-C CCS being included in the 2013 PROMs survey. However, the FACT-C CCS demonstrated its ability to distinguish between these patient groups, despite the overall FACT-C measure not being validated for use specifically in LRRC, as described in chapter 2. Moreover, both datasets reported only cross-sectional HrQoL data, prospective reporting allows for more meaningful HrQoL assessment, as HrQoL trajectories and their correspondence with clinical changes can be evaluated. Overall, these issues emphasise the need to further develop and standardise the inclusion of HrQoL data within colorectal cancer registries, particularly for patients with advanced or recurrent disease. The inclusion of patients undergoing pelvic exenteration for LARC within NBOCA is a positive development and expansion to include patients with LRRC would be an important area for future work. In relation to

capturing HrQoL in this setting, this should be undertaken using disease-specific PROMs such as the LRRC-QoL. Improving and building on the availability of high-quality HrQoL registry data for patients with LRRC, collected using validated disease-specific measures, would enable greater exploration of the impact of LRRC on HrQoL at a national level.

11.3.2 Cross-Cultural Adaptation and External Validation of the LRRC-QoL

A significant strength of the work in this thesis is its impact on the reporting of HrQoL in LRRC through cross-cultural adaptation (chapter 5) and external validation (chapter 6) of the LRRC-QoL. This has resulted in a measure validated for use in 14 countries and represents a significant advancement in the potential to report international HrQoL outcomes in LRRC using a disease-specific, vigorously developed and validated measure. The study demonstrates the capacity to successfully complete cross-cultural adaptation and external validation in rare disease settings. The involvement of low- and middle-income countries also demonstrates the ability to undertake such studies across varied healthcare systems. The breadth of languages and countries included within this process confirm that LRRC-QoL is relevant, acceptable, and provides a valid assessment of HrQoL in patients with LRRC on a broad international platform.

In relation to the cross-cultural adaptation of the LRRC-QoL (chapter 5), a robust methodological approach was applied which included translatability assessment, forward and backward translation involving clinicians with experience treating patients with LRRC and professional translators. This was followed by pre-testing cognitive interviews with patients and healthcare professionals, and utilisation of the QQ-10 measure to assess

the face validity and acceptability of the LRRC-QoL. The meticulous nature of this approach has resulted in measures which demonstrate conceptual equivalence across all versions, in addition to confirming the content validity, face validity, and acceptability of the measure. The international approach to the external validation of the LRRC-QoL is a significant strength of the study. Though this is not the classical approach for external validation studies, conducting a multinational study is essential in rare disease settings to reach a sample enabling robust psychometric analyses (290). Furthermore, the wide range of languages and countries represented in the analysis confirm the generalisability of the externally validated measure.

A major limitation of this work was the inability to implement significant changes across all versions of the LRRC-QoL following cross-cultural adaptation. This was not possible due to the inclusion of responses to the cross-cultural adaptation study in the external validation analysis. This methodological approach was undertaken given the limited timeframe for recruitment and anticipated challenges in accruing the number of participants required for external validation. Though this is a limitation of the study, the pre-testing cognitive interviews identified very few changes to implement to the measure, meaning it did not significantly affect the outcome. The four suggested changes to the measure could be addressed in several ways. The suggestions to add a skip question prior to the Urinary Symptoms scale for patients with a urostomy and prior to the Sexual Interest and Function scales for patients who are not sexually active, could also be addressed through the addition of a “N/A” response option for these items. Currently there are no “N/A” response options within the overall measure and patients are advised not to respond to scales which are not relevant to them. This presents challenges in relation to identifying whether data is missing at random, or the items were not relevant

to the patient, the addition of a "N/A" option would help clarify. The major limitation to this approach is that further testing of the face validity of the LRRC-QoL would be required if these changes are implemented. The other two changes related to the naming of scales and were discussed with the original developers of the LRRC-QoL. The suggestion to rename the female Sexual Function items, given that they relate predominately to gynaecological symptoms rather than sexual function, was ultimately not adopted. Though acknowledged as accurate, it was felt that adding further titles or subheadings above the scale would be confusing, particularly given that the items for male patients do relate to sexual function. No female patients participating in either the original development of the LRRC-QoL or the cross-cultural adaptation interviews reported issues relating specifically to female sexual function. Therefore, it was not deemed appropriate to reflect this in the overall measure. Finally, the suggestion to change the name of the Urostomy scale to reflect its inclusion of nephrostomies, catheters, or other urinary devices, will be implemented across all versions of the LRRC-QoL. This change is unlikely to affect the content or face validity of the measure and will therefore not require further pre-testing cognitive interviews.

A significant challenge in completing the cross-cultural adaptation of the LRRC-QoL was meeting the recruitment target of 10-15 patients per language advised by the EORTC QLG (110). Though the small numbers of patients recruited for some versions of the questionnaire are a limitation to the study, in a rare disease setting this is an appropriate and recognised approach (290). Completing this component of the study and moving to workstream II, the prospective, longitudinal study (chapter 7), could have been undertaken sooner if this approach had been adopted more widely and should be considered in the development of future versions of the LRRC-QoL.

The most significant limitation of the study overall is the failure to reach the recruitment target of 320 patients for the external validation of the LRRC-QoL. This resulted in not being able to conduct CFA for all nine scales of the measure, even in a combined cohort of 321 patients from the original and external validation studies. The inclusion of scales, such as the Urostomy or gender-specific Sexual Function scales, which only apply to specific subgroups of patients, means an even greater sample size for CFA is required, which is challenging to achieve in this rare disease setting. The reduced sample size may also have affected other aspects of the psychometric analysis, including the reliability analysis, particularly for the Urostomy and gender-specific Sexual Function scales which are only relevant to subgroups of patients. However, these scales demonstrated excellent reliability in the original development of the LRRC-QoL. Despite the limitations described, recruiting 204 patients with LRRC remains a significant achievement and the LRRC-QoL demonstrated excellent psychometric properties overall.

11.3.3 Identifying the Long-Term Survivorship Issues Relevant to Patients with LRRC

The strengths and limitations of the mixed-methods study to identify long-term survivorship issues in LRRC are reported in detail in chapter 8. Overall, a major strength of the study is the inclusion of an international sample of patients, meaning the results can be considered generalisable for patients treated for LRRC in Western Europe, North America, and Australasia. The central limitation of the study was the use of the LRRC-QoL conceptual framework (106) to inform the interview topic guide, however, this was not felt to have impacted on the results of the thematic analysis significantly.

11.3.4 Optimising Recruitment to Studies in LRRC

The utilisation of a modified QRI to explore recruitment challenges and implement strategies to address them in a structured and systematic approach was a significant strength of the study. Though recruitment to research studies in advanced or recurrent cancer, such as LRRC, are known to be challenging (302, 360), a targeted approach to examine and tackle these difficulties has not previously been reported. As such, one of the key benefits of this work is its potential to shape future research practices in LRRC. Though limited by the lack of qualitative methodology in the modified QRI applied, implementing this component would have been particularly challenging given the research climate during the main study setup period in 2020 and 2021 (355).

11.4 Implications Moving Forwards

11.4.1 The LRRC-QoL Measure

The LRRC-QoL should now be considered the gold standard for assessing HrQoL in LRRC in both clinical and academic settings. It is the only disease-specific measure of HrQoL for patients with LRRC and has demonstrated robust psychometric properties in the original validation and international, external validation analyses described within this thesis. The LRRC-QoL has been adapted for use on an international scale, including countries in Europe, Asia, North America, South America, and Australasia; meaning it can be used across many populations.

11.4.1.1 Applications of the LRRC-QoL

There are numerous ways in which the LRRC-QoL could improve clinical care for patients with LRRC. Many of these have previously been described and include its

potential in guiding discussions between patients and clinicians and in clinical decision making processes (108). However, realising the full extent of the benefits to be gained from utilising the LRRC-QoL in both clinical and academic settings can only be achieved if routinely implemented. Though both patients and clinicians consider PROs to be valuable in the context of advanced colorectal cancer (46), there are several barriers to consistent PROMs data collection in clinical practice (394). These can include resource allocation and practical challenges related to implementation, clinicians not being engaged or lacking awareness regarding PROMs and their interpretation, with associated training needs (394). The optimum approach would be to mandate the administration of the LRRC-QoL at the point of diagnosis with LRRC and at regular intervals during treatment and follow-up on a national or even international scale. Introducing compulsory PROMs data collection would oblige clinicians and healthcare providers to engage with this process and provide a framework and resources to enable its delivery. The feasibility of this approach within the NHS is evident in the national PROMs programme (395). Collecting LRRC-QoL data in an observational clinical study setting, as evidenced in this thesis, presents many challenges, with a recruitment rate of 50% representing an achievement. It is possible that completion rates would be lower if the LRRC-QoL were to be presented to both clinicians and patients as a routine aspect of clinical care opposed to within a research study. In patients undergoing elective hip and knee replacement procedures within the English NHS, baseline response rates to the national PROMs programme were 69.5% and 65.4% respectively between April 2021 and March 2022 (279). Replicating these rates in LRRC is likely to be difficult given the more burdensome nature of the disease. Compulsory PROMs collection within the NHS would reach a greater proportion of patients with LRRC, though targeted efforts, such as those described in chapter 10, may be required to achieve high response rates.

One of the ways in which mandatory data collection utilising the LRRC-QoL could be applied is to monitor symptoms within follow-up care. Remote web-based symptom monitoring using PROMs has been shown to improve QoL (130) and even overall survival (131, 132) across a range of malignancies. Integrating the LRRC-QoL within existing care pathways offers the potential to replicate these significant benefits in the management of patients with LRRC. Online versions of the LRRC-QoL in English, Dutch, and Danish, administered via REDCap, were developed during this study, and represent a significant first step in delivering LRRC-QoL ePROMs. Linking the LRRC-QoL ePROM with clinical systems would facilitate routine utilisation of the measure within follow-up, allowing for remote monitoring of symptoms prompting intervention from healthcare professionals when required. The utilisation of the LRRC-QoL within follow-up could extend into long-term survivorship care, as demonstrated in the findings of the survivorship work in chapter 8. This will also enable longitudinal, prospective HrQoL reporting from baseline diagnosis with LRRC through to long-term survivorship utilising the LRRC-QoL measure, allowing for comparison of outcomes at various timepoints and between groups.

Additionally, further analysis could be undertaken utilising the baseline HrQoL data collected during the studies described in chapters 6 and 7 to assess whether baseline HrQoL, as determined by the LRRC-QoL, serves as a prognostic indicator. PROs including physical functioning and HrQoL have previously been identified as independent predictors of overall survival across a number of malignancies (396). Regarding LRRC, previously identified predictors of HrQoL include gender, bony resection, and baseline HrQoL, in patients undergoing surgery (98). These predictors would benefit from further evaluation in an external cohort and in patients undergoing treatment with palliative intent.

11.4.1.2 Implications for Future Clinical Trials and Meaningful Interpretation of LRRC-QoL Scores

Utilisation of the LRRC-QoL to measure HrQoL as an endpoint in clinical trials will enable the evaluation of treatments for LRRC from a patient-centred perspective in combination with traditional clinical outcomes such as survival. The HrQoL data collected using the LRRC-QoL during the studies described in this thesis could be used as reference data with several potential applications for future studies and RCTs. Interpretation of the LRRC-QoL and its scale scores would be enhanced through the calculation of MIDs. MIDs are the smallest difference in score which can be perceived as important to patients, prompting consideration of a change in management (397); thus enabling the interpretation of HrQoL data in a clinically meaningful way. The data collected in this thesis could be used in future studies to establish MIDs for the LRRC-QoL and its scales. Different approaches can be undertaken to establish MIDs, including anchor-based and distribution-based methods. Anchor-based methods, incorporating clinician-rated and patient-rated variables, are the recommended approach to estimating MIDs (398). This involves selecting anchor variables, such as clinical measures or patient ratings, which are associated with a change in the PRO of interest, with a recommended 0.30-0.35 correlation threshold between anchor and PRO change score (398). Groups of patients are then identified depending on their degree of change in the anchors identified (398). Comparisons of changes in PRO scores across the identified groups can then be used to establish MIDs (307, 398).

A further application of reference HrQoL data is in informing sample size calculations for RCTs. A range of methods can be used for sample size calculations generally and also

specifically in relation to PROs as primary outcomes, where different approaches have been described (399). These include methods utilising previous study or trial data to analyse changes in HrQoL pre- and post-intervention or randomisation (399). An important component of sample size calculations is the target difference for the primary outcome (400), in RCTs utilising PROMs as a primary outcome measure, MIDs are advised for use as the target difference (401). The data reported in this thesis could therefore be used to inform sample size calculations for RCTs in LRRC and in establishing MIDs for the LRRC-QoL, as described above.

11.4.2 Reporting PROs in LRRC

11.4.2.1 Selection of PROMs

The LRRC-QoL is undoubtedly now established as the most appropriate measure of HrQoL in LRRC, being the only PROM to demonstrate content validity for this purpose and given its strong psychometric properties. However, the question remains as to whether other existing PROMs should continue to be utilised in patients with LRRC. A significant issue related to the selection of PROMs is their ability to compare both across and within specific groups of patients. The LRRC-QoL was developed in keeping with EORTC guidelines (293), with a view to its use as a disease-specific measure combined with the EORTC QLQ-C30 in a modular approach. This approach would therefore allow for comparison of outcomes across different groups of patients utilising the EORTC QLQ-C30 whilst ensuring disease-specific HrQoL is captured by the LRRC-QoL. The LRRC-QoL has also demonstrated its ability to compare sub-groups of patients with LRRC and respond to clinical change. Once patients reach 12-months post treatment, the EORTC SURV100 should then be used in combination with the LRRC-QoL to report

long-term HrQoL outcomes. This approach is strongly supported by the results of the survivorship study described in chapter 8.

Comparing contemporaneous LRRC-QoL data to historic HrQoL data in patients with LRRC poses additional difficulties given the wide range of measures reported, as evidenced in chapter 2. The FACT-C has demonstrated excellent psychometric properties in primary colorectal cancer (201) and has been widely used to report outcomes in LRRC. Its lack of confirmed content validity for use in this specific context renders it impossible to definitively recommend its ongoing use in principle. However, chapter 3 of this thesis illustrates the ability of the FACT-C to differentiate HrQoL outcomes in patients with PRC and LRRC. Existing evidence reporting HrQoL utilising the FACT-C should not be disregarded, given that the FACT-C has demonstrated its ability to identify HrQoL differences in patients with LRRC. However, it is unlikely to demonstrate the magnitude of the impact of LRRC on HrQoL, as it does not comprehensively assess the HrQoL issues which are relevant to patients with LRRC (106).

In relation to comparisons with data collected using different PROMs, statistical models or algorithms can be used to map scores from one PROM to another, this approach is most frequently employed to enable cost-utility analysis through mapping PROMs to the EQ-5D (402). The performance of algorithms mapping the EORTC QLQ-C30 to the EQ-5D have previously been evaluated in patients with metastatic colorectal cancer, reporting that existing algorithms performed well in this context (403). These algorithms are likely to also be appropriate for data collected using the EORTC QLQ-C30 in the context of LRRC and could be used in cost-utility analyses.

11.4.2.2Registry HrQoL Data in LRRC

The propensity score matched study described in chapter 3 highlights several areas for development regarding the inclusion of HrQoL data in colorectal cancer registries. Additionally, data regarding patients with LRRC are not currently captured in national registries such as NBOCA or CORECT-R, representing a significant limitation. Collecting and including PROMs data within existing national registries has numerous benefits which are evident in the context of joint replacement surgery, as detailed in chapter 3.

In relation to cancer care, national registries have an important role in documenting variation in care and access to treatments; information which can then be used to drive improvements in patient outcomes (404). The value of national cancer registries is apparent in the recent formation of the National Cancer Audit Collaborating Centre (NATCAN) within the Royal College of Surgeons (RCS) of England (404). Existing audits including NBOCA are delivered through this initiative, accompanied by the creation of five new national cancer audits (404). Linkage of these audits with PROMs data collection at a national level has numerous potential applications, including comparison of HrQoL outcomes within sub-groups of patients based on clinical variables, across regions, and to population norms. Collecting PROMs data online offers additional benefits, as demonstrated by the NHS Cancer Quality of Life Survey (405). Aggregated, anonymised survey data is available publicly online (406, 407), enabling patients to access a summary of their responses compared with the general population (406), which can be used at an individual patient level to inform encounters with healthcare professionals.

The ability to collect national HrQoL data in patients with colorectal cancer has previously been demonstrated through the 2013 NHS PROMs survey (244, 408). The subsequent linkage of this data to both NBOCA and CORECT-R (243, 255), demonstrates the feasibility of introducing mandatory prospective PROMs data collection and linkage to national colorectal cancer registries. In addition to the potential applications described above, this could also enable comparison of PROs across NHS Trusts. This data could in turn be used to improve service delivery by the same mechanisms applied for clinical outcomes through NBOCA (231). Routine capture of clinical and PROMs outcome data within national registries should also be extended to patients with LRRC. Mandating PROMs data collection utilising the LRRC-QoL would facilitate this process in addition to the clinical benefits this would offer, as previously highlighted. The LRRC-QoL is the ideal measure for this purpose, as previously highlighted. Including the EORTC QLQ-C30 as a generic measure in addition to the disease-specific LRRC-QoL would also enable comparison with other patient groups or even potential linkage to the NHS Cancer Quality of Life Survey dataset.

Collecting and utilising clinical and HrQoL registry data is likely to present additional challenges in the context of LRRC. During recruitment to the prospective cohort study described in chapter 7, one of the difficulties encountered during screening and approaching patients was confirming a true diagnosis of LRRC. The term “recurrence” was frequently documented in MDT lists for patients who have developed a regrowth following neoadjuvant treatment, which does not meet the BeyondTME consensus definition of LRRC (1), and caused confusion when not appropriately verified. Careful coding is crucial to ensuring this cohort of patients are appropriately captured within colorectal cancer registries, and sources such as Hospital Episode Statistics (HES) may

not provide sufficient detail to accurately report the complexity of advanced or recurrent rectal cancers and their management (409).

Patient experiences of healthcare are an equally important consideration in evaluating care from a more holistic and patient-centred perspective. These outcomes are captured by PREMs which have been assessed at a national level since 2010 in England through the Cancer Patient Experience Survey (CPES). Data from CPES is intended to aid commissioners and care providers, inform quality improvement initiatives, in addition to informing charities and stakeholder groups in supporting patients (410). In relation to colorectal cancer patients, results from the 2015 CPES have been cross-linked to NBOCA with a report published in 2020 (411). A subset of patients who had been admitted to hospital close to the time of receiving a colorectal cancer diagnosis were identified to evaluate the potential utility of CPES data as a performance indicator (411). The patient experience outcomes were generally positive in patients with colorectal cancer and the CPES overall care score was found to have good clinical validity as a performance indicator (411), suggesting it could be used to evaluate quality of care. Patient experience outcomes have not previously been reported in LRRC. Introducing mandatory administration of the LRRC-QoL would capture patient experiences through the Healthcare Services scale, in addition to reporting HrQoL. As highlighted in chapter 7, patients receiving treatment for LRRC reported worse healthcare experiences over time. Examining the experiences of patients with LRRC at a national level through mandatory PROMs data collection would further build on this evidence and facilitate the development of strategies to improve patient care. Incorporating both PROMs and PREMs within colorectal cancer registries routinely, both generally and specifically for patients with LRRC utilising the LRRC-QoL, would be an immensely valuable addition

to assessing the quality of care delivery from a holistic perspective and could be used to drive patient-centred improvements in outcomes.

11.4.2.3Standardising Outcome Reporting in LRRC

In terms of standardising outcome reporting, including HrQoL outcomes, the lack of a core outcome set (COS) specifically for LRRC was highlighted during the LRRC-QoL development (108). This is due to change with a COS for LRRC having been recently registered in the Core Outcome Measures in Effectiveness Trials (COMET) initiative database. Previous work in patients with advanced colorectal cancer suggests that HrQoL is likely to be identified as an outcome for inclusion (15), in which case the LRRC-QoL would be the unrivalled choice of disease-specific outcome measure. HrQoL has also been identified during the Delphi process in developing a COS for empty pelvis syndrome (ClinicalTrials.gov Identifier: NCT05683795). The LRRC-QoL is currently the most appropriate measure to capture HrQoL and issues related to empty pelvis syndrome in patients with LRRC who have undergone exenterative surgery. Features of empty pelvis syndrome, such as perineal wound breakdown (148, 412), would be captured through items such as “Have you had pain or discharge from your wound(s) or scar(s)?”.

11.4.3 Survivorship Care in LRRC

As highlighted in the first chapter of this thesis, there is increasing focus on survivorship across the cancer care continuum. Recent years have seen particular focus on delivering personalised and patient-centred care through treatment, follow-up, and longer-term survivorship. Personalised Care and Support Planning (PCSP) is a process of care delivery which “*ensures people’s physical, practical, emotional and social needs are identified and addressed at the earliest opportunity*” (413, 414). From a follow-up care

perspective, Personalised Stratified Follow Up (PSFU) pathways are being introduced to colorectal cancer follow-up to offer a more holistic and personalised approach in addition to routine monitoring for recurrence (415). Central components of PSFU include a shared decision-making process between patients and clinicians to undertake either remote monitoring or face-to-face clinic appointments, informing patients of signs and symptoms of recurrence, rapid access to their cancer team if needed, and support for self-management (415).

Survivorship care in LRRC is relatively underreported due to historically poor survival outcomes. The mixed-methods study reported in chapter 8 demonstrates the similarities in the survivorship issues experienced by longer-term survivors of LRRC and patients who are closer to diagnosis, suggesting that many of these issues could be identified and addressed within routine follow-up care. In relation to improving the delivery of personalised care for LRRC survivors, many of the interventions highlighted in relation to PCSP and PSFU could also be applied in relation to follow-up care for patients with LRRC. The nature of LRRC and its treatment is complex and heterogenous, surgical resection is meticulously planned and tailored to the individual patient and their pattern of recurrence, with a view to achieving an R0 resection. Therefore, delivering personalised follow-up care in this setting is highly pertinent given the individualised nature of LRRC and its treatment. End of Treatment Summaries are advocated within PSFU to provide patients and their GP with information regarding their cancer treatment, details of side effects, signs of recurrence and contact details for their cancer care team (413, 414). From an international perspective, this has significant overlap with guidance regarding survivorship care plans (120). In the context of LRRC, End of Treatment Summaries could also prove a valuable source of support to both patients and GPs during

the transition from specialist follow-up to primary care considering the complexities of LRRC treatment.

Regarding the LRRC-specific survivorship issues identified in this thesis, recognising and managing these issues within follow-up care could be achieved through screening utilising the LRRC-QoL PROM as described above. Patients found to be experiencing specific issues could then be reviewed by the clinical team, offered self-management advice, or referred for specialist treatment if required. Other strategies, including dedicated survivorship clinics, online survivorship interventions, and survivorship care plans have been investigated across a range of primary malignancies (124, 126, 335, 416). These approaches have not been explored in LRRC and represent potential areas for future research. Internationally, the work reported by Lim et al. in Sydney, Australia, represents an important contribution to the literature regarding survivorship in LRRC (142-145). Future research projects to develop survivorship care interventions in this setting could be explored via a collaborative approach given the precedent of working with this team throughout the original development (392) and external validation of the LRRC-QoL. In addition to national and international collaborative networks, including PelvEx, UKPEN, and IMPACT. Alternative approaches include developing interventions at a local or regional level, this may be more appropriate in a survivorship context to ensure that models of care are specific to the needs of local populations and services (126).

11.4.4 Lessons for Future Clinical Studies and Trials in LRRC

The process of setting up and running the studies described within this thesis offers a number of important learning points for future multinational studies of HrQoL in LRRC.

Chapter 9 details the challenges experienced whilst setting up the study and highlights key areas to optimise these processes. These include highlighting common issues which arise during the implementation of Data Sharing Agreements with international sites and strategies to address them. For example, agreeing to remain silent on the court of jurisdiction which will govern the agreement. Regarding the implications of Brexit, this process is now much clearer from a legal perspective following the EU's recognition of UK data protection standards as adequate (351). Setup of the study required gaining multiple ethical approvals from each participating site and/or country. Though many of these processes inherently lack efficiency, means to optimise them were identified, including frequent communication, high levels of organisation in maintaining and circulating local information packs, and careful consideration during translation processes for study documents to ensure accuracy and avoid wasting resources. In the future, central ethical approval via the EU CTIS may streamline these processes further.

From a recruitment perspective, the utilisation of a modified QRI identified several successful strategies to improve recruitment rates which should be implemented in future studies of HrQoL. These include undertaking PPI work in the development of PILs, streamlining and centralising recruitment processes, including undertaking verbal consent for the central research team to contact patients directly. Additionally, offering multiple options for PROM completion, including paper-based, online, and via telephone, and maintaining regular communication with sites regarding recruitment.

As highlighted, the expertise and experience of researchers undertaking studies in patients with LRRC represent an important source of evidence to inform future projects. The experiences of studies currently underway, such as the GRECCAR 15 (82) and PelvEx II

(44) trials and a study to develop a decision aid for patients with LRRC and LARC (417) will further expand this knowledge base. This could also be explored further through undertaking qualitative work with research teams and patients to further elicit potential challenges and solutions to drive improvements in study design prior to implementation. The strategies described may also be valuable in other rare disease settings, particularly in studies reporting HrQoL.

11.5 Conclusion

The core themes of this thesis, namely HrQoL and survivorship in LRRC, have been explored through the studies described within. Particularly through the cross-cultural adaptation and international validation of the LRRC-QoL and qualitative exploration of long-term survivorship issues. The LRRC-QoL measure is now accessible to a wide range of patients, with versions existing in 10 languages for use in 14 countries. The confirmation of its psychometric properties and establishment of its responsiveness to clinical change, have important implications for reporting of HrQoL in LRRC, for which the LRRC-QoL should now be considered the gold standard measure in both clinical and academic settings. Establishing MIDs for the LRRC-QoL and its scales would further enhance its utility in future clinical studies and would facilitate sample size calculations. The growing body of evidence regarding longer term survivorship in LRRC has been advanced through the identification of survivorship issues in an international setting. Future work to report prospective, long-term HrQoL in LRRC will further understanding of the long and lasting impact of LRRC and its treatment.

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Appendix 1: Search Strategy

(locally AND recurrent AND (rectal neoplasm [MeSH Terms] OR cancer of the rectum OR rectal cancer OR rectal tumour))

AND

(((patient-reported AND outcome*) OR (patient-reported AND outcome* AND measure) OR (PROM*))

OR

((quality of life [MeSH Terms] OR (quality AND life) OR quality of life) OR (health-related quality of life OR ((health [MeSH Terms] OR health) AND related AND quality of life))

OR

(symptom AND prevention and control [Subheading])

OR

(questionnaires [MeSH Terms] OR questionnaires)).

Appendix 2: Lay Summary for the Registry-Based Study Comparing HrQoL between patients with PRC and LRRC

In the UK there are over 40,000 cases of bowel cancer every year and almost a third of those cases occur in the lowest part of the bowel, the rectum. Primary rectal cancer and its treatment can have a significant impact on a patient's quality of life and patients may experience long-term issues following treatment such as altered bowel function, sexual function, or urinary function. Locally recurrent rectal cancer (LRRC) is when a patient's cancer returns following surgery somewhere within the pelvis. LRRC occurs in 5-10% of rectal cancer cases. When such cancer comes back the patient can suffer considerable pain and it is likely to reduce a patient's quality of life. Also, treatment of LRRC may itself reduce the patient's quality of life. A study of patients in the Netherlands suggested that patients with LRRC have worse quality of life than patients with primary rectal cancer. A similar Danish study found that quality of life was initially worse in patients with LRRC but by 12-months it was similar to those who had not developed a recurrence.

This study used data collected in two previous studies. The first was a study of quality of life in patients treated for bowel cancer in England, the second was a study to develop a questionnaire specifically to measure quality of life in patients with LRRC. This data was combined to compare quality of life outcomes between patients with primary rectal cancer and LRRC. The study found that patients with LRRC reported worse overall quality of life compared to patients with primary rectal cancer, experiencing worse stomach swelling, more diarrhoea, worse digestion and appetite, and less control over their bowels. However, patients with LRRC reported greater satisfaction with the appearance of their

body. We hope that these results will help guide discussions with patients regarding their treatment and the effect it may have on their quality of life.

Appendix 3: LRRC-QoL Measure Following Validation in the UK and Australia and Translatability Assessment

For office use only
Participant number: _____ Participant initials: ____ Follow-up interval: _____

Locally Recurrent Rectal Cancer Quality of Life Questionnaire

(LRRC-QoL)

This questionnaire asks your views about the impact that the recurrence of rectal cancer in the pelvis has had on your everyday life during the past few weeks, including symptoms, sexual function, psychological impact, role functioning and healthcare services.

Please answer all the questions yourself. There are no right or wrong answers.

The information that you provide will remain strictly confidential.

Thank you for taking the time to complete this questionnaire.

LRRC-QoL

We are interested in some things about you and your health. Please answer all the questions by yourself by circling the number that best applies to you. There are no right or wrong answers.

Pain **During the *PAST WEEK:***	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
1. Have you had abdominal pain?.....	1	2	3	4
2. Have you had pain in your lower back and/or pelvis?.....	1	2	3	4
3. Have you had pain in your buttocks/anal area/rectum?.....	1	2	3	4

Urinary Symptoms **During the *PAST WEEK:***	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
4. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
5. Have you had any unintentional release (leakage) of urine?	1	2	3	4

Lower Limb Symptoms **During the *PAST WEEK:***	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
6. Have you had any weakness of either or both legs?.....	1	2	3	4
7. Have you had any difficulty in walking?.....	1	2	3	4
8. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4

Other Symptoms

During the *PAST WEEK:*

Do you still have a rectum or anus? Yes.... please answer Question 9. No.... please go to Question 10.	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
9. Have you had any abnormal bleeding, discharge or faecal leakage from your rectum?.....	1	2	3	4
10. Have you had pain or discharge from your wound(s) or scar(s)?.....	1	2	3	4

11. Do you have a stoma?

Yes...Please go to Question 12
No....Please go to Question 14

Stoma

During the *PAST WEEK:*

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
12.Have you felt embarrassed because of your stoma?.....	1	2	3	4
13. Have you had any problems caring for your stoma?.....	1	2	3	4

14. Do you have a urostomy (urine bag), nephrostomy or urinary catheter?

Yes...Please go to Question 15

No....Please go to Question 18

Urostomy

During the *PAST WEEK:*

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
15. Did you have problems caring for your urostomy (urine bag), nephrostomy or urinary catheter?.....	1	2	3	4
16. Have you felt embarrassed because of your urostomy (urine bag), nephrostomy or urinary catheter?.....	1	2	3	4
17. Have you been dependent on others for caring for your urostomy (urine bag)?.....	1	2	3	4

Sexual Interest

During the *PAST 4 WEEKS:*

	Not at all	A little	Quite a Bit	Very much
18. Have you been interested in sex?	1	2	3	4
19. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4

Sexual Function

During the *PAST 4 WEEKS:*

	Not at all	A little	Quite a Bit	Very much
For women only:				
20. Have you had any abnormal discharge or bleeding from your vagina?	1	2	3	4
21. Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
For men only:				
22. How difficult is it for you to gain or maintain an erection?	1	2	3	4
23. Have you had ejaculation problems (e.g. dry ejaculation)?	1	2	3	4

Psychological Impact

During the *PAST 4 WEEKS:*

	Not at all	A little	Quite a Bit	Very much
24. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
25. Do you worry about the results of examinations and tests?.	1	2	3	4
26. Do you worry about possible future treatments?	1	2	3	4
27. Have you felt uncertain about the future?	1	2	3	4

	Not at all	A little	Quite a Bit	Very much
28. Have you worried about becoming dependent on others because of your illness?	1	2	3	4

Healthcare Services
During the *PAST 4 WEEKS:*

	Not at all	A little	Quite a Bit	Very much
29. Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?	1	2	3	4
30. Were you satisfied with the knowledge and experience of your specialist team (Doctors/ Nurses/Specialist Nurses/ Physiotherapists)?	1	2	3	4
31. Were you satisfied with the speed of implementing medical tests and/or treatments?	1	2	3	4

Date questionnaire completed: _____

Appendix 4: Cross-Cultural Adaptation Interview Topic Guide

Cross-Cultural Adaptation Interview Guide

For the cross-cultural adaptation interviews, these may be undertaken at sites following discussion with the research team and using the following guide. The research team may oversee one of the interviews or one interview will be recorded to ensure consistency across interviews.

Please could the interviewer complete the feedback form during the interview.

For **each set of questions** in the questionnaire, ask the participant:

1. Is this experience relevant to your disease or treatment?
2. Were any of these questions difficult to answer?
3. Were any of these questions confusing?
4. Were any of these questions difficult to understand?
5. Were any of these questions upsetting or offensive?
6. If there are any comments regarding a question, ask the participant:
    a. How would you ask this question in your own words?

For the **questionnaire as a whole:**

1. Were there any questions that you found to be irrelevant?

If the patient completed an online version of the questionnaire, please also complete the relevant questions.

Following this please complete the QQ-10 with the patient.

Cross-Cultural Adaptation Interview Feedback

Questions	Yes	Feedback
Pain		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Urinary Symptoms		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		

Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Lower Limb Symptoms		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Other Symptoms		
Is this experience relevant to your disease or treatment?		

Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Stoma		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Urostomy		

Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Sexual Interest		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		

How would you ask these questions in your own words?		
Sexual Function		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Psychological Impact		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		

Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Question 28		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		
Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
Healthcare Services		
Is this experience relevant to your disease or treatment?		
Were any of these questions difficult to answer?		
Were any of these questions confusing?		

Were any of these questions difficult to understand?		
Were any of these questions upsetting or offensive?		
How would you ask these questions in your own words?		
For the Questionnaire as a whole:		
Were there any questions that you found to be irrelevant?		
If the patient completed the Questionnaire online, please ask the following questions:		
Was the electronic platform easy to use?		
Was the electronic platform easy to navigate?		
Were the instructions difficult to understand?		
Are there any ways in which the electronic platform could be improved?		
Please now complete the QQ-10 with the patient.		

Appendix 5: Operation Performed for LRRC in External Validation Cohort

Operation performed for LRRC	Workstream I: Cross-cultural adaptation (n=67) (%)	Workstream II: Prospective Cohort (n=137) (%)	Combined Cohort (n=204) (%)
Operation performed for LRRC			
Abdominal and ischioanal excision with vertical rectus abdominis myocutaneous (VRAM) flap	1 (2.1)	0 (0.0)	1 (0.9)
Anterior exenteration including colpectomy, coccygectomy and cytoreductive surgery, partial small bowel resections with S-S anastomosis, omentectomy and Bricker	0 (0.0)	1 (1.6)	1 (0.9)
Anterior resection	6 (12.8)	3 (4.8)	9 (8.3)
Anterior resection and para-aortic lymph node dissection	0 (0.0)	1 (1.6)	1 (0.9)
Abdominoperineal resection (APER)	3 (6.4)	5 (8.1)	8 (7.3)
APER, resection of vagina, VRAM flap and hysterectomy	1 (2.1)	0 (0.0)	1 (0.9)
APER and S5 sacrectomy	0 (0.0)	1 (1.6)	1 (0.9)
APER, S4 sacrectomy and right gracilis muscles, perineal reconstruction	0 (0.0)	1 (1.6)	1 (0.9)
APER, S2 sacrectomy, bilateral internal iliac artery and vein ligation and gluteal flap reconstruction	0 (0.0)	1 (1.6)	1 (0.9)
APER and hysterectomy	1 (2.1)	0 (0.0)	1 (0.9)
Beyond TME rectal re-excision with left hypogastric vein resection, left ureteric resection and reconstruction	1 (2.1)	0 (0.0)	1 (0.9)
Colorectal re-excision and partial prostatectomy	1 (2.1)	0 (0.0)	1 (0.9)
Cystectomy, sacrectomy and left pelvic sidewall resection	0 (0.0)	1 (1.6)	1 (0.9)
Cystoprostatectomy, pelvic sidewall resection, VRAM flap and ileal conduit	1 (2.1)	0 (0.0)	1 (0.9)
En bloc resection of the prostate and rectum, vesico-ureteral anastomosis and coloanal anastomosis	1 (2.1)	0 (0.0)	1 (0.9)

Extralevator pelvectomy and S3/4 sacrectomy	1 (2.1)	0 (0.0)	1 (0.9)
Laparoscopic extended TME with presacral fascia and loop ileostomy	0 (0.0)	1 (1.6)	1 (0.9)
Laparoscopic TME, resection of seminal vesicles, presacral fascia and right pelvic sidewall	0 (0.0)	1 (1.6)	1 (0.9)
Laparotomy and redo anterior resection with en bloc resection of vaginal vault	0 (0.0)	1 (1.6)	1 (0.9)
Laparotomy, ultralow Hartmann's with en bloc resection of seminal vesicles	0 (0.0)	1 (1.6)	1 (0.9)
Laparotomy, ureteric re-implantation, LRRC not resectable	1 (2.1)	0 (0.0)	1 (0.9)
Left pelvic sidewall clearance, oophorectomy and appendicectomy	1 (2.1)	0 (0.0)	1 (0.9)
Left pelvic sidewall resection including internal iliac, resection of presacral fascia and coccyx, left nephrectomy and IORT	1 (2.1)	0 (0.0)	1 (0.9)
Local excision of perineum and flap	1 (2.1)	0 (0.0)	1 (0.9)
Low anterior resection with seminal vesicles en bloc	0 (0.0)	1 (1.6)	1 (0.9)
Open excision of LRRC including pelvic sidewall and caecum	0 (0.0)	1 (1.6)	1 (0.9)
Open partial cystectomy and right oophorectomy	0 (0.0)	1 (1.6)	1 (0.9)
Open pelvic exenteration, bilateral pelvic sidewall clearance distal to superior gluteal artery, S2/3 sacrectomy, total vaginectomy, ileo-caecectomy, ileal conduit and perineal right inferior gluteal artery perforator (IGAP) flap	0 (0.0)	1 (1.6)	1 (0.9)
Pelvic exenteration	4 (8.5)	1 (1.6)	5 (4.6)
Pelvic exenteration and VRAM flap	1 (2.1)	0 (0.0)	1 (0.9)
Pelvic exenteration, S2 sacrectomy, cystoprostatectomy, small bowel resection, right hemicolectomy, ileal conduit, V-Y advancement flap right buttock	0 (0.0)	1 (1.6)	1 (0.9)
Posterior exenteration and coloanal anastomosis	1 (2.1)	0 (0.0)	1 (0.9)
Posterior exenteration, bilateral sacral ligaments and muscles (SLAM) excision, left pelvic sidewall clearance, S4 sacrectomy, left ischial spine	0 (0.0)	1 (1.6)	1 (0.9)

excision, reversal of loop ileostomy and right gluteal flap			
Posterior exenteration, resection of presacral fascia and bilateral ureteric reimplantation	1 (2.1)	0 (0.0)	1 (0.9)
Posterior exenteration, vagal nerve resection, sciatic nerve resection, S5 sacrectomy	1 (2.1)	0 (0.0)	1 (0.9)
Redo total pelvic exenteration (TPE) with S2 sacrectomy en bloc with small bowel resection, wide perineal excision with left gluteus excision, bilateral extended lateral pelvic sidewall excision (ELSiE), V-Y left superior gluteal artery perforator (SGAP) flap	0 (0.0)	1 (1.6)	1 (0.9)
Rectal re-excision	0 (0.0)	5 (8.1)	5 (4.6)
Rectal re-excision with ureteric re-implantation	0 (0.0)	1 (1.6)	1 (0.9)
Resection of LRRC and IORT	1 (2.1)	1 (1.6)	2 (1.8)
Sacrectomy	0 (0.0)	1 (1.6)	1 (0.9)
Pelvic sidewall dissection and right groin dissection	0 (0.0)	1 (1.6)	1 (0.9)
Pelvic sidewall dissection and ureteric re-implantation	0 (0.0)	1 (1.6)	1 (0.9)
TPE	3 (6.4)	8 (12.9)	11 (10.1)
TPE and sciatic nerve resection	1 (2.1)	0 (0.0)	1 (0.9)
TPE and subcortical dissection S1-3, cystoprostatectomy	1 (2.1)	0 (0.0)	2 (1.8)
TPE, right ELSiE, total vaginectomy, right S4 hemisacrectomy	0 (0.0)	1 (1.6)	1 (0.9)
TPE, vesico-ureteral anastomosis and coccygectomy	1 (2.1)	1 (1.6)	2 (1.8)
TPE and abdominal wall reconstruction	0 (0.0)	1 (1.6)	1 (0.9)
TPE and left ELSiE	0 (0.0)	1 (1.6)	1 (0.9)
TPE and pelvic sidewall resection	0 (0.0)	1 (1.6)	1 (0.9)
TPE including presacral fascia, small bowel resection and IORT	0 (0.0)	1 (1.6)	1 (0.9)
TPE with lymph node dissection and VRAM flap	0 (0.0)	1 (1.6)	1 (0.9)
TPE, bilateral ELSiE, subperiosteal dissection L5, S4 sacrectomy, parastomal hernia repair, right SGAP flap	0 (0.0)	1 (1.6)	1 (0.9)
TPE, left bony ELSiE, high sacrectomy, ileal conduit	0 (0.0)	1 (1.6)	1 (0.9)

TPE, right ELSiE, resection of piriformis, total sciatic nerve, coccyx and presacral dissection	0 (0.0)	1 (1.6)	1 (0.9)
Ultralow anterior resection, bilateral salpingo-oophorectomy, vaginectomy, loop ileostomy	1 (2.1)	0 (0.0)	1 (0.9)
Wide local excision with left urinary diversion	1 (2.1)	0 (0.0)	1 (0.9)
Unknown	9 (19.1)	8 (12.9)	17 (15.6)

Appendix 6: Scoring Instructions for the LRRC-QoL

Pain Scale

Overall scale score = Item 1 + Item 2 + Item 3

Score range 3-12, higher scores indicate worse pain symptoms.

Urinary Symptoms Scale

Overall scale score = Item 4 + Item 5

Score range 2-8, higher scores indicate worse urinary symptoms.

Lower Limb Symptoms Scale

Overall scale score = Item 6 + Item 7 + Item 8

Score range 3-12, higher scores indicate worse lower limb symptoms.

Stoma Scale

Overall scale score = Item 12 + Item 13

Score range 0-8, scale should be skipped if patient does not have a stoma, higher scores indicate worse stoma-related issues.

Urostomy Scale

Overall scale score = Item 15 + Item 16 + Item 17

Score range 0-8, scale should be skipped if patient does not have a urostomy, nephrostomy, or catheter. Higher scores indicate worse urostomy/urinary device-related issues.

Sexual Interest Scale

Overall scale score = Item 18 + Item 19

Score range 2-8, higher scores indicate higher levels of sexual interest and worse pain during sexual activity.

Female Sexual Function Scale

Overall scale score = Item 20 + Item 21

Score range 2-8, higher scores indicate worse vaginal symptoms.

Male Sexual Function Scale

Overall scale score = Item 22 + Item 23

Score range 2-8, higher scores indicate worse erectile and ejaculatory function.

Psychological Impact Scale

Overall scale score = Item 24 + Item 25 + Item 26 + Item 27

Score range 4-16, higher scores indicate worse psychological impact.

Healthcare Services Scale

Overall scale score = Item 29 + Item 30 + Item 31

Score range 3-12, higher scores indicate better healthcare experiences.

Stand-alone Items

Item 9, score range 0-4, can be skipped if not relevant (patient no longer has rectum or anus in situ) higher score indicates worse symptoms.

Item 10, score range 1-4, higher score indicates worse symptoms.

Item 28, score range 1-4, higher score indicates worse symptoms.

Health-related Quality of Life (HrQoL) Score

Overall score = Pain scale score + Urinary Symptoms scale score + Lower Limb Symptoms scale score + Item 9 + Item 10 + Stoma scale score + Urostomy scale score + Sexual Interest scale score + Gender-specific Sexual Function scale score + Psychological Impact scale score + Item 28

Score range 18-96, higher score indicates worse HrQoL.

Appendix 7: Data Completeness for the LRRC-QoL Items in the Prospective Cohort Study

	Baseline			3-months			6-months		
	N	**Missing (%)**	**Mean (SD)**	**N**	**Missing (%)**	**Mean (SD)**	**N**	**Missing (%)**	**Mean (SD)**
43. Abdominal pain	101	0 (0.0)	1.61 (0.77)	75	0 (0.0)	1.69 (0.87)	59	0 (0.0)	1.68 (0.80)
44. Lower back/ pelvic pain	101	1 (1.0)	1.77 (0.87)	75	1 (1.33)	1.80 (0.92)	59	0 (0.0)	1.92 (0.97)
45. Perianal/ buttock pain	101	1 (1.0)	1.75 (1.00)	75	1 (1.33)	1.95 (1.11)	59	0 (0.0)	2.08 (1.10)
46. Urinary irritation	101	0 (0.0)	1.43 (0.83)	75	1 (1.33)	1.30 (0.61)	59	0 (0.0)	1.32 (0.63)
47. Urinary incontinence	101	1 (1.0)	1.48 (0.73)	75	1 (1.33)	1.58 (0.84)	59	0 (0.0)	1.44 (0.77)
48. Lower limb weakness	101	0 (0.0)	1.64 (0.87)	75	0 (0.0)	1.93 (1.06)	59	0 (0.0)	1.97 (1.05)
49. Difficulty in walking	101	1 (1.0)	1.65 (0.88)	75	0 (0.0)	1.89 (1.01)	59	0 (0.0)	1.98 (1.12)
50. Lower limb numbness	101	1 (1.0)	1.75 (1.00)	75	0 (0.0)	1.99 (1.12)	59	0 (0.0)	2.10 (1.08)
51. Leakage/discharge from rectum	101	32 (31.7)	1.61 (0.77)	75	37 (49.3)	1.63 (0.82)	59	33 (55.9)	1.62 (0.90)
52. Pain/discharge from wounds	101	23 (22.8)	1.26 (0.57)	75	17 (22.7)	1.59 (0.92)	59	9 (15.3)	1.46 (0.76)
14. Embarrassment from stoma	67	0 (0.0)	1.85 (0.88)	64	0 (0.0)	1.66 (0.84)	50	0 (0.0)	1.60 (0.76)
15. Problems caring for stoma	67	5 (7.46)	1.56 (0.80)	64	5 (7.81)	1.46 (0.65)	50	5 (10.0)	1.42 (0.69)

32. Problems caring for urostomy	11	0 (0.0)	1.82 (0.75)	17	0 (0.0)	1.65 (0.70)	19	0 (0.0)	1.89 (0.99)
33. Embarrassment from urostomy`	11	0 (0.0)	1.45 (5.2)	17	1 (5.88)	1.75 (0.93)	19	0 (0.0)	1.58 (0.77)
34. Dependent on others for caring for urostomy	11	1 (9.09)	1.60 (0.70)	17	2 (11.8)	1.67 (0.82)	19	0 (0.0)	1.79 (0.92)
35. Interest in sex	101	3 (3.0)	1.60 (0.85)	75	2 (2.67)	1.49 (0.69)	59	5 (8.47)	1.50 (0.69)
36. Pain during sexual intercourse	101	26 (25.7)	1.19 (0.51)	75	32 (42.7)	1.19 (0.50)	59	25 (42.4)	1.21 (0.64)
37. Discharge or bleeding from vagina (women)	32	1 (3.13)	1.39 (0.62)	19	1 (5.26)	1.39 (0.85)	17	2 (11.8)	1.60 (1.12)
38. Irritation or soreness in vagina or vulva (women)	32	3 (9.34)	1.38 (0.82)	19	2 (10.5)	1.24 (0.56)	17	2 (11.8)	1.13 (0.35)
39. Erectile function (men)	69	4 (5.80)	2.85 (1.27)	56	8 (14.3)	2.96 (1.18)	42	8 (19.0)	3.00 (1.21)
40. Ejaculatory dysfunction (men)	69	5 (7.25)	2.23 (1.39)	56	16 (25.6)	2.45 (1.41)	42	8 (19.0)	2.62 (1.42)
41. Attractiveness	101	0 (0.0)	2.13 (1.02)	75	0 (0.0)	2.12 (0.94)	59	1 (1.69)	2.05 (1.02)
42. Worry about results	101	0 (0.0)	2.47 (0.99)	75	0 (0.0)	2.41 (1.02)	59	0 (0.0)	2.47 (1.09)
43. Worry about future treatments	101	0 (0.0)	2.66 (1.00)	75	0 (0.0)	2.41 (1.02)	59	0 (0.0)	2.56 (1.04)
44. Uncertainty about the future	101	0 (0.0)	2.78 (1.06)	75	0 (0.0)	2.52 (1.03)	59	0 (0.0)	2.54 (1.10)
45. Worry about becoming dependent	101	0 (0.0)	2.58 (1.07)	75	0 (0.0)	2.37 (1.01)	59	0 (0.0)	2.36 (1.08)
46. Satisfaction with information	101	0 (0.0)	3.49 (0.73)	75	1 (1.33)	3.24 (0.84)	59	0 (0.0)	3.15 (0.81)

47. Satisfaction with knowledge	101	0 (0.0)	3.62 (0.66)	75	1 (1.33)	3.46 (0.71)	59	0 (0.0)	3.29 (0.87)
48. Satisfaction with speed of implementation	101	0 (0.0)	3.29 (0.85)	75	1 (1.33)	3.18 (0.85)	59	0 (0.0)	2.97 (0.96)

Appendix 8: Qualitative Survivorship Interview Guide

Identifying survivorship themes relevant to LRRC survivors

Throughout the interview, open-ended questions will be used to identify survivorship and HrQoL themes. Cognitive probes will be used to explore the themes raised by participants in more detail with both open-ended and closed-ended questions.

1. **Introduction**
    a. Explain the aim of the interview.
    b. Explain that everything discussed will be confidential and that anonymised quotations may be published.
    c. Explain that the participant can withdraw/terminate the interview at any time.
2. **Survivorship:**
    a. What is your experience following successful treatment for LRRC?
    b. What have been the challenges and difficulties you have experienced following treatment for LRRC?
        i. What have been the good things you have experienced?
        ii. What would you change following your experience?
    c. What has been your experience of follow-up care after LRRC?
        i. What have been the good things you have experienced?
        ii. Is there anything in your experience that you would change?
3. **Impact on HrQoL:**
    a. Explore the themes identified in the LRRC-QoL conceptual framework:
        i. Symptoms – if not discussed in survivorship – pain, urinary symptoms, lower limb symptoms, stoma-related, urostomy-related

ii. Sexual function

iii. Psychological impact – Role functioning – work, social, relationships

iv. Future perspectives – disease recurrence, future plans

v. Healthcare services utilisation and delivery

4. End of the interview:

a. Thank participant

b. Explain how the topics discussed in the interview will be analysed

c. Any further questions?