The Development and Validation of a Patient-Reported Outcome Measure of Health-Related Quality of Life in Locally Recurrent Rectal Cancer

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I dedicate this thesis to the women who have helped shape my life with their love, support and encouragement – my beloved, late grandmother Baa, my mother Pushpa and my sister Vina.

Abstract

Background

The impact of locally recurrent rectal cancer (LRRC) on health-related quality of life (HrQoL) is poorly understood. The overall aim of the project was to develop and validate a patient reported outcome measure (PROM) to assess HrQoL in LRRC in patients in the UK and Australia. This thesis reports on the initial development of the LRRC-QoL and the results from the interim psychometric analysis from the UK cohort.

Methods

An international, three phase, mixed methodological study was conducted. Phase I consisted of two systematic reviews and a qualitative study consisting of a series of focus groups. Phase II consisted of the development and pre-testing of the provisional PROM; The Locally Recurrent Rectal Cancer Quality of Life Measure (The LRRC-QoL). Phase III assessed the psychometric properties of the LRRC-QoL including scale structure, reliability and validity.

Results

Phase I: Relevant HrQoL themes were identified; symptoms, sexual function, psychological impact, role functioning, healthcare services, future perspective. These themes were operationalised into a conceptual framework and reviewed by an expert panel prior to the development of a provisional version of the LRRC-QoL.

Phase II: A total of 27 cognitive interviews were undertaken to pre-test the LRRC-QoL. The measure underwent three revisions in both population cohorts. The final version of the LRRC-QoL ready for psychometric testing consisted of 32 questions organised into 5 scales.

Phase III: Eighty patients participated in the UK validation study. The final scale structure consisted of healthcare services, psychological impact, sexual function, pain, urostomy-related symptoms, lower limb symptoms, stoma related issues, sexual interest and urinary symptoms.

The reliability of the LRRC-QoL was good, with Cronbach's Alpha and Intraclass correlation values of >0.7 for the majority of the scales. The LRRC-QoL was unable to demonstrate the properties of convergent validity and known-groups comparison sufficiently.

Conclusions

The LRRC-QoL is the first measure to be developed exclusively in patients with LRRC. The scale structure of the LRRC-QoL is robust. Further work is required including the completion of the psychometric validation in Australia and the confirmation of reliability and validity in an independent sample.

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List of Abbreviations

BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
CES-D	Centre for Epidemiologic Studies Depression Scale
CASM	Cognitive Aspects of Survey Methodology
CONSORT	Consolidated Standards of Reporting Trials
CAPS	Critical Appraisal Skills Programme Checklist
EORTC QLQ-CR38	European Organisation for Research and Treatment of Cancer - Colorectal Module
EORTC QLQ-CR29	European Organisation for Research and Treatment of Cancer - Colorectal Module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Core Questionnaire
EBRT	external beam radiotherapy
FDA	U.S. Food and Drug Administration
FACT-C	Functional Assessment of Cancer Therapy - Colorectal
FIQL	Faecal Incontinence Quality of Life
GI	gastrointestinal
HrQoL	health-related quality of life
IGRT	image-guided radiotherapy
IES-R	Impact of Events Scale-Revised
IADL	Instrumental Activities of Daily Living
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISOQOL	International Society for Quality of Life Research
IORT	intraoperative radiotherapy
LARC	locally advanced rectal cancer
LASC	locally advanced sigmoid cancer
LRRC	locally recurrent rectal cancer
MDT	multidisciplinary team
NHS	National Health Service
NOS	Newcastle-Ottawa Scale
PPE	partial pelvic exenteration
PROMS	Patient Reported Outcome Measures
PROs	patient-reported outcomes
QoL	quality of life
QAS-99	Question Appraisal System-99
SF36	Short Form 36
SF-12	Short-Form 12
SQOLS	Stoma Quality of Life Scale
SBRT	stereotactic body radiation therapy
TPE	total pelvic exenteration

1 Chapter One – Introduction

1.1 Introduction

The period between the 1980s and the early 2000s witnessed improvements in the surgical technique and the use of multimodal treatments in the management of primary rectal cancer. The success of these advances translated clinically as a reduction in the incidence of local (pelvic) recurrence of rectal cancer from 30-40% to 5-10%[1-4]. Unsurprisingly, attention has since been directed towards advancing the surgical management of locally recurrent rectal cancer (LRRC). It is estimated that approximately 700 patients present each year within the UK with LRRC, of which 50% of patients will be suitable for surgical resection [5]. These small but significant numbers of patients represent a significant challenge to the National Health Service (NHS) with regards to optimal treatment and management strategies. As a consequence a number of international bodies have pooled together their expertise to develop international guidelines to inform the clinical decision-making in this cohort of patients [6, 7].

1.2 Locally Recurrent Rectal Cancer

Local recurrence following previous 'curative' resection of primary rectal cancer is defined as 'tumour recurrence in the previous operative field within the pelvis' [8, 9]. The majority of local recurrences present within the first 3 years of the primary surgery [10]. A third of recurrences are asymptomatic and are detected during routine post-operative follow up examination. Pelvic pain, rectal bleeding, discharge, change in bowel habit and non-healing perineal wounds may all be symptoms of recurrent disease. It is estimated up to 50% of patients with local recurrence present with synchronous metastatic disease.

1.2.1 Classification

Pelvic recurrences following rectal cancer have been categorised according to their anatomical location by a number of authors. The Leeds group defined pelvic recurrences as central (confined to pelvic organs without bony involvement), sidewall (involving pelvic sidewall structures), sacral (abutting onto or involving the sacrum), or composite (involving sacral and sidewall structures) [8]. The Mayo Clinic described recurrence in terms of degree of fixation both in terms of site (anterior, sacral, right or left) and number of points of fixation (F0-3) [11]. The Memorial Sloan Kettering group classified recurrences as axial (anastomotic recurrence after low anterior resection, perineal recurrence following APR and local recurrence following transanal excision), anterior (involving urological and/or gynaecological structures), posterior (involving the sacrum and/or coccyx) and lateral (involving pelvic sidewall structures) [12]. Wanebo et al based their classification of local recurrence upon the UICC TNM system; with TR1 and TR2 tumours corresponding to intraluminal recurrences following local excision or at the anastomosis, TR3 corresponding to recurrence at or around the level of the anastomosis with limited extramural spread and without pelvic fixation; TR4 corresponds to invasion into either adjacent urogenital structures or presacral tissues with tethering but no fixation and TR5 corresponding to invasion into the sacrum or pelvic sidewall [13]. For the purposes of this thesis all patients will be classified in accordance with the anatomical location of their disease recurrence; anterior (involving the urogenital organs), posterior (involving the sacrum and/or coccyx), central (involving the neo-rectum or rectal stump) and lateral (involving the pelvic sidewall structures).

1.2.2 Treatment

Treatment strategies are complex in LRRC, with treatment decisions often following on from the treatment strategy received during the treatment of the primary rectal cancer. A multimodal approach, including surgery, chemotherapy and radiotherapy, is often incorporated in the management of LRRC following multidisciplinary team meeting. Although, there are no formal guidelines on the

management of LRRC, The Beyond TME collaborative group, consisting of surgeons, oncologists, radiologists and pathologists, published a consensus statement on best clinical practice in this cohort of patients. This consensus statement included algorithms to help guide management (Figures 1.1 and 1.2).

The treatment decisions in this cohort of patients are often complex, and require a multidisciplinary approach, with appropriate input from surgeons (colorectal, urologists, gynaecologists and plastics), radiologists, oncologists and palliative care medicine physicians. Current National Institute of Health and Care Excellence only outline the role of MDTs in the management of patients with metastatic colorectal cancer, with no specific recommendations for the discussion of LRRC within this forum [14]. Previous works on the role of the MDT in recurrent disease for oesophageal cancer identified that a smaller than expected number of patients were being referred for further discussion. However, of those who were referred for further discussion active management in the form of palliative chemotherapy +/- radiotherapy, oesophageal stenting or surgery was offered to over fifty per cent of patients. The role and importance of MDTS is amplified in difficult disease settings, such as LRRC, where treatment decisions can be complex, with a variety of potential options available and where treatment goals can range from cure to best supportive care. There is limited research on the role of MDTs specifically in LRRC, however, Kontovounisios et al reported improved patient selection for surgery and consequently improved clinical and surgical outcomes for locally advanced and recurrent rectal cancer, when patients were discussed in a dedicated specialist MDT at a tertiary referral centre. The importance of MDT discussion for locally advanced and recurrent colorectal cancer has recently been acknowledged by the Association of Coloproctology of Great Britain and Ireland, and has identified this as a key area for improvement, with a view to developing an advanced cancer MDT.

Surgery

The aims of operative intervention are primarily to achieve cure, with a curative R0 resection achieved in 40-50% of patients undergoing surgery [15]. In select circumstances operative

intervention may be reserved to achieve palliation with treatment aims based on symptom control, prolongation of life and improvement of health-related quality of life (HrQoL).

Curative Surgery

The main aim of curative surgery in LRRC is to obtain a negative (R0) resection margin. A R0 resection margin confers optimal survival benefit in this cohort of patients when compared to a microscopically (R1) or macroscopically (R2) positive margin [15].

Traditionally, there have been a number of absolute and relative contraindications to surgery. The absolute contraindications include the presence of unresectable metastatic disease and frailty precluding general anaesthesia. Relative contraindications include high sacral involvement above the level of S3, extensive lateral pelvic sidewall involvement, extension through the greater sciatic notch and 360 degree encasement of the iliac vessels [8]. Being guided by these recommendations, a number of authors have reported 5-year survival rates of 25-50% in patients undergoing surgical resection of LRRC combined with multimodal treatments [16-18]. This survival benefit must be offset against the high risks carried with surgical intervention with 30-day morbidity and mortality quoted at 15-68%. In a bid to further improve clinical outcomes in this cohort of patients combined with affording cure to a greater proportion of patients, an emphasis has been placed on ultra-radical resection, thus rendering these relative contraindications obsolete [19]. This has been accelerated due to vast improvements in surgical techniques and critical care services combined with an emphasis on the surgical multidisciplinary team within the operating theatre. The preliminary evidence in this cohort of patients is encouraging with 5 year survival rates of 17-31% in high sacrectomy [13, 20-22], 62% in external hemipelvectomy[23] and upto 52% in lateral pelvic sidewall resection[24-26], however, the rates of morbidity have been documented to be 31-70%.

Palliative Surgery

Palliative surgery for LRRC is controversial with no additional survival benefit conferred by surgery when compared to palliative oncological treatments [15]. In the complex scenario of advanced pelvic

recurrence not amenable to curative resection surgical intervention is reserved for palliation and control of symptoms in selected cases. Palliative surgical resection offers the most benefit in patients with bleeding, obstruction, pelvic sepsis and intractable pelvic pain [27, 28].

Post-operative Outcomes

Irrespective of the intent of surgery, i.e. curative or palliative, surgery in this cohort of patients is associated with high post-operative burden. Due to the extensive nature of operative intervention post-operative recovery is often long and associated with a high rate of complications. Thirty day post-operative morbidity is estimated between 15-68%, with pelvic sepsis and post-operative wound complications being the most common [18]. Further intervention, either radiological or surgical is often required to adequately and effectively deal with post-operative complications [29]. Thirty-day post-operative mortality is high, with an estimated rate of 1-15% [18]. These risks are significantly higher than that conferred by operative management in primary rectal cancer, with the National Bowel Cancer Audit reporting a 90-day mortality rate of 3.2% in patients undergoing a major resection for rectal cancer [30]. These short-term burdens of post-operative recovery must be balanced against the goals of surgery, any potential benefit conferred by survival and the risk of re-recurrent disease.

Multimodal Treatments

It is desirable to incorporate a multimodal approach in combination with operative intervention, with the emphasis being on the incorporation of chemotherapy +/- radiotherapy within the treatment algorithm. However, the use of multimodal treatments in LRRC is often dictated by the treatments received during the management of primary rectal cancer and on the goals of treatment (i.e. curative or palliative).

In the curative setting, patients with LRRC who are radiotherapy naive are usually treated with pre-operative chemoradiation. However, it is the management of the cohort of patients, who have previously received radiotherapy that is contentious due to the concerns of potential higher rates of

morbidity encountered secondary to the high cumulative radiation doses to normal structures with further radiation. As a result, there have been a number of radiotherapy techniques that have been developed to circumvent the potential hazards of additional delivery of external beam radiation, including, intra-operative radiotherapy, brachytherapy and image-guided radiotherapy.

Re-irradiation

The role of re-irradiation with external beam radiotherapy (EBRT) in combination with surgery has been explored by some authors, with re-irradiation doses of 30Gy associated with a reported 5-year survival of 19-25% [31-33]. However, there are concerns with use of re-irradiation due to the cumulative effects of radiation toxicity, with initial rates of acute and late toxicity reported to be 25-32% and 36-38% respectively[32, 33]. To circumvent the relatively high rates of radiation toxicity observed with the use of EBRT in the reirradiation of LRRC, a group of authors have explored the use of reirradiation with hyperfractionated chemoradiation with encouraging results. Valentini et al reported a grade 3 acute toxicity rates of 5.1% with no grade 4 toxicity observed in 51 patients completing a hyperfractionated radiotherapy schedule of 1.2Gy twice daily, with a cumulative dose of 40Gy, with concurrent infusion of 5-fluorouracil [34]. Similarly, Das et al treated 50 patients with a hyperfractionated accelerated regimen of 1.5Gy, with a cumulative dose of 39Gy, with concurrent capecitabine [35]. This group reported a 4% rate of grade 3/4 acute toxicity. In combination with a lower rate of radiotherapy related toxicity, this group of authors reported a statistically significant link between response to re-irradiation and the ability to perform a radical resection ($p=0.009$).

In the palliative setting, the use of reirradiation with EBRT has been found to effectively palliate and control symptoms, with Mohiuddin et al reporting effective palliation of symptoms of bleeding in 100% of patients for a median period of 10 months, pain in 55% and tumour mass in 25% for a median period of 9 and 8 months respectively [31]. Lingareddy presented similar rates of palliation of symptoms in 52 patients undergoing palliative reirradiation, with effective palliation of symptoms in 80% of patients, using a regimen of 1.2Gy fractions twice a day or 1.8Gy once daily, up to a median dose of 30Gy, with selective boost doses of 6-20Gy [36].

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) is a specialist technique of delivering irradiation at the time of surgery. Over the past three decades, two alternative but complementary IORT methods; intraoperative electron radiation therapy and high-dose rate brachytherapy, have evolved into technically sophisticated treatments with the central philosophy of achieving higher effective doses of irradiation whilst limiting radiation to surrounding normal tissues. The advantage of incorporating IORT into the radiotherapy treatment algorithm for LRRC is the precise application and delivery of radiation to 'at risk areas' for further disease relapse.

The use of IORT was first reported by Gunderson et al in the 1980s, this group reported the combined used of ERBT and IORT in 51 patients with locally advanced or recurrent colorectal cancer, reporting an overall 5 year survival of 23% in the recurrent disease group [37]. Local failure rate within the IORT field was 2% and within the external beam field was 18% [37]. This study provided encouraging data for the incorporation of IORT into the multimodal strategy for LRRC, leading to a number of investigators to explore the addition of IORT to surgery +/- chemoradiation [38-53], with reported 5 year local control rates of 26-74% and 5 year survival rates of 11-49.5% [54-70]. The largest series of IORT in combination with EBRT +/- chemotherapy was reported by Haddock et al in 607 patients, with 5 year central relapse rate of 14% within the IORT field, a local relapse rate of 28% and overall 5 year survival of 30% [70].

Local control rates observed in the IORT series are 26-81% which are comparable, if not slightly superior to the rates observed in the non-IORT series at 41- 67% [71-74]. A number of authors have demonstrated good rates of disease control within the actual IORT field, with reported rates of central control of 53-93% [61, 65, 67, 70]. Nuyttens et al observed a greater number of out of IORT field recurrences than in field recurrences (7 versus 5), with out of field recurrences occurring earlier at a median time of 16 months compared to 31 months with in field recurrences (p=0.077) [67]. This observation has been echoed by a number of other authors, which adds to the evidence base, that IORT provides high rates of local control. To reduce the rate of out of field recurrences, further

studies are required to investigate the role of expanding the IORT field and/or increasing the dose of IORT delivered.

IORT is most commonly reserved for use in the curative surgical setting with limited reports in the palliative surgical setting. Suzuki et al exclusively reported outcomes in patients undergoing palliative resection of LRRC in combination with IORT, with improved rates of 3 year overall survival and local disease relapse rates in the IORT group versus the non-IORT group[51].

It is difficult to elicit the true IORT related complication rates in the majority of studies, due to the differences in reporting complication rates, with some studies reporting IORT related complication separately, whilst others combine surgical and IORT related complications. Peripheral neuropathy and ureteral stenosis have emerged as IORT-related complications from the literature, with rates of 7-34%[56, 75] [48, 54, 55, 60] and 6.4-36% [44, 46, 56, 60] respectively.

Brachytherapy

Brachytherapy is the implantation of radioactive sources within or close to malignant lesions, which enable the delivery of radiation directly to the site of the tumour. In the treatment of LRRC, temporary iridium-192 or permanent implantable iodine-125 is used as the radiation source. In temporary implantation applicators are implanted intraoperatively, with delivery of radiation in the post-operative period. The advantages of interstitial implantation include the higher delivery of radiation, combined with limitation of damage to surrounding normal tissue structures due to the sharp dose fall off outside the implanted volume.

The evidence base for brachytherapy in LRRC is mainly limited to the treatment with palliative intent following surgical debulking in the presence of microscopic or macroscopic residual disease. This is not a common modality of treatment for this cohort of patients. The documented local control rates with brachytherapy are variable, with reported rates of 8 – 64%, with an associated complication rate of 10-45% [76-82].

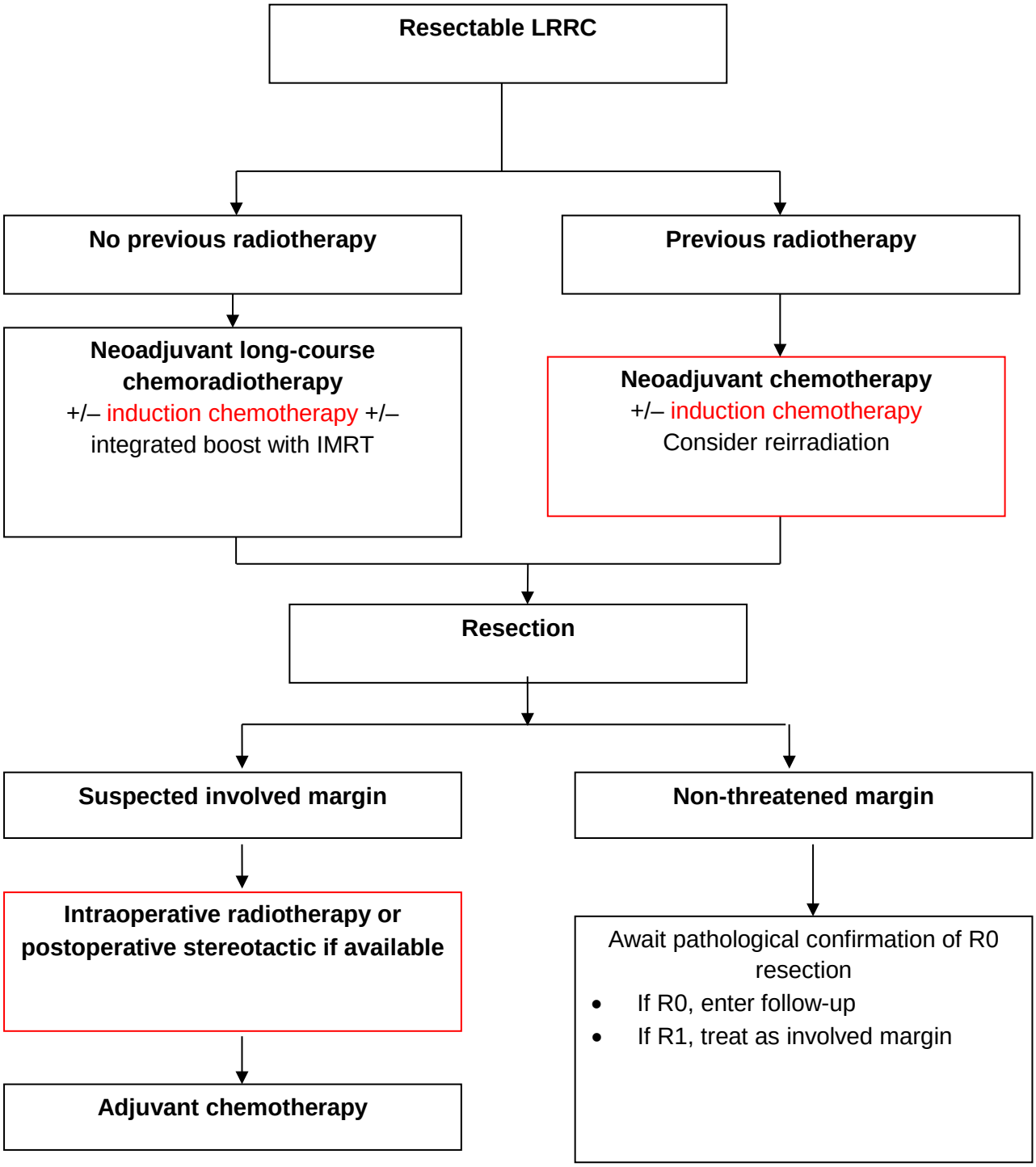
Highly Conformal Stereotactic Radiotherapy

Emerging radiotherapy techniques such as image-guided radiotherapy (IGRT) combined with improvements in radiotherapy software and hardware have led to the development of Cyberknife, tomotherapy and linear accelerator based stereotactic body radiation therapy (SBRT). These techniques permit precise radiotherapy planning and the delivery of highly conformed radiation beams to the target volume along with real time visualisation of target volumes and normal tissues during treatment delivery. This precise visualisation of anatomical structures combined with reduced treatment volumes allows for the precise delivery of radiotherapy, thus limiting radiotherapy induced damage to normal anatomical structures. However, this technology is in its infancy with only a few reports in the palliative setting with regards to LRRC.

Kim et al investigated the use of Cyberknife in inoperable nodal recurrences in 23 patients [83]. Five patients were treated with a combination of EBRT (45Gy in 1.8Gy fraction) followed by a stereotactic single fraction radiotherapy boost (16Gy). 18 patients were treated with SBRT alone, with a median dose of 39Gy (IQR 36-51) delivered in 3 fractions. This group reported an overall 5 year survival rate of 23.3%, with a 4 year actuarial local progression free survival rate of 74.3%. Grade 4 toxicity was observed in 1 (4.3%) patient. No complications were observed in 4 patients who underwent reirradiation.

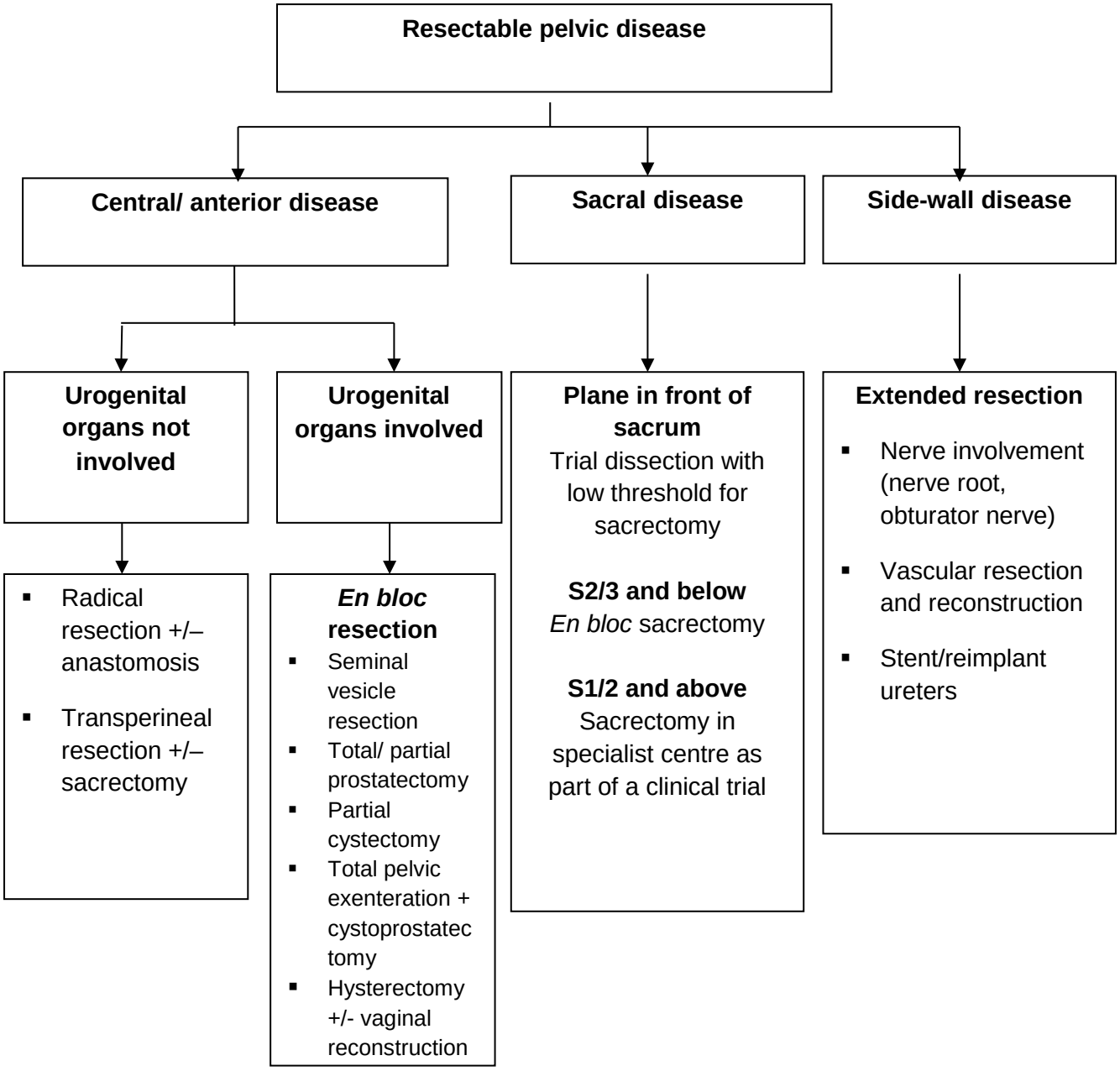
Dewas et al reported their experience of reirradiation using Cyberknife in 16 patients with recurrent inoperable pelvic malignancy, 4 of whom had recurrent rectal cancer[84]. The median dose of the previous radiotherapy treatment was 45Gy (IQR 20-96). Patients were treated with a total dose of 36Gy in six fractions over a three week period. No grade 3 or 4 acute toxicity was observed in this group. One year local control rate was 51.4% with a one year survival rate of 46%.

Figure 1-1 Guidance for the use of chemoradiotherapy in LRRC – BeyondTME guidance [6]



* Boxes in red represent areas of controversy. IMRT – intensity modulated radiotherapy.

Figure 1-2 Management options for pelvic resectable pelvic disease – BeyondTME guidance [6]



1.2.3 Locally Recurrent Rectal Cancer – Future Directions?

LRRC represents a heterogeneous group of patients who are extremely complex to manage, often requiring a tailored management approach. The management options available to these patients are often dependent on local referral pathways alongside local expertise and resources available [5].

The current evidence base comprises of level 2 and 3 grade evidence, consisting of single centre case studies and cohort studies. Given the heterogeneous nature of LRRC, conducting a large-scale, multi-centre randomised controlled trial to inform clinical practice has been acknowledged to be extremely difficult [7]. To circumvent this and in an attempt to standardise the management of patients with LRRC two expert panels have developed a set of guidelines to aid management decisions in this cohort [6, 7]. These two comprehensive reviews of the current evidence base identified a number of key areas to focus on to improve outcomes including the standardisation of outcome measures, measuring the cost-effectiveness of interventions and reporting on HrQoL.

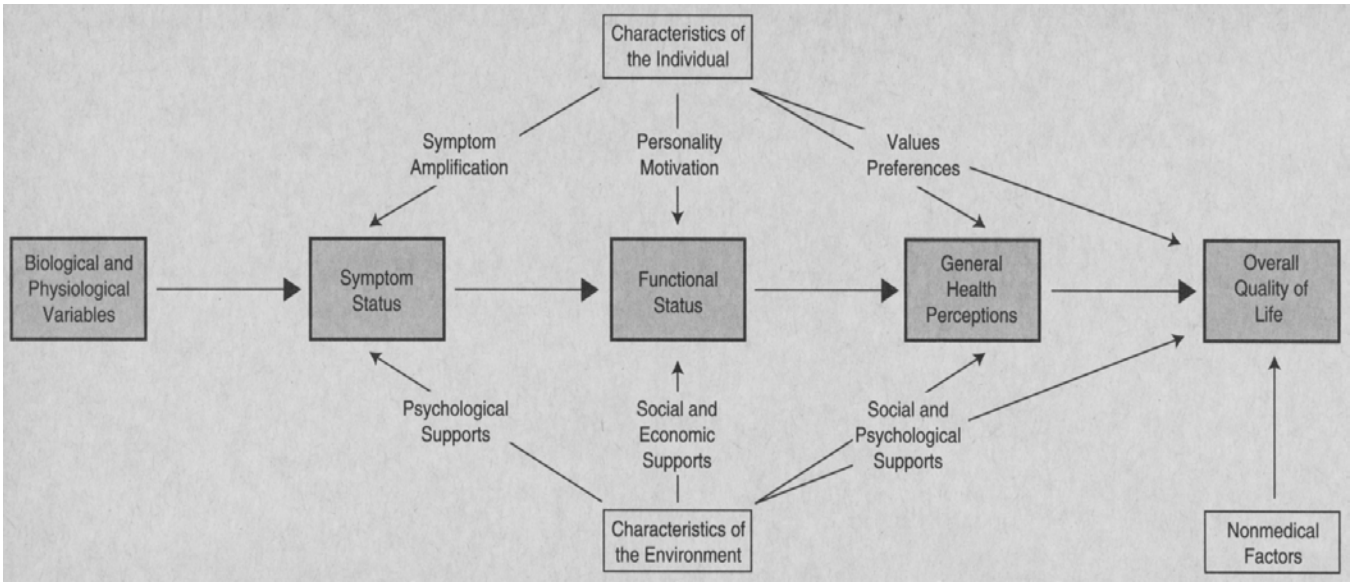
As the management strategy for LRRC continues to evolve, with an increasing emphasis placed on achieving cure for a greater proportion of patients through the use of extended surgical resection combined with aggressive multimodal therapies [19, 85], it is essential the impact on patients is reported. The traditional markers of success such as morbidity, mortality, survival and re-recurrence need to be extended to include patient-reported outcomes (PROs), specifically HrQoL [6, 7] to provide a more broad and robust perspective in this cohort of patients.

1.3 Measurement of Health Status and Health Outcomes

The traditional model of measuring health status relied on the presence or absence of disease, with traditional health outcomes based on clinical markers of morbidity, mortality and survival. The steady evolution of health outcomes measurement has led to significant attention and consideration being given to PROs to include quality of life (QoL) and HrQoL in the reporting of outcomes in oncology and chronic diseases [86-88]. The US Food and Drug Agency (FDA) define a PRO as ‘a measurement based on a report that comes directly from the patient about their health condition without amendment

or interpretation of the patients response by a clinician or anyone else' [89]. The term QoL was developed by the World Health Organisation and is defined as an 'individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'. It is a broad concept affected by an individual's physical health, psychological state, level of independence and social relationships. HrQoL is defined as the extent to which one's physical, emotional and social well being are affected by a medical condition or its treatment [90]. HrQoL is a complex, multi-dimensional construct which includes dimensions of physical functioning, social functioning, role functioning, mental health and general health perceptions, with additional dimensions, including symptom status, functional status and characteristics of the individual and environment [91-93]. PRO and HrQoL data is best interpreted within its clinical context alongside clinical and oncological outcomes [88]. This is reflected in a number of conceptual models for HrQoL, including the Wilson and Cleary model, which incorporates biological and psychological aspects of health outcomes (Figure 1.3) [93]. The Wilson and Cleary model consists of five core levels, which includes biological and physiological factors, symptoms, functioning, general health perceptions and quality of life. In addition to these levels, this model proposes a number of causal relationships between these levels, thus linking traditional clinical variables and measures of HrQoL and switching the emphasis of measuring health status from a biomedical model to a patient-centred model. Utilising this conceptual model to measure health status and its outcome provides clinicians and policy-makers a unique insight into the patient perspective of disease impact and its outcome.

Figure 1-3 The Wilson and Clearly Model of HrQoL



1.3.1 PROMS Measurement in the NHS

Patient Reported Outcome Measures (PROMS) were initially highlighted within the NHS by Lord Darzi in the NHS Next Stage Review Report in 2008 [94]. This review acknowledged the role of PROMS data in the evaluation of healthcare and the potential to use this data to guide regulatory decision-making. Following this review, the NHS PROMS programme was introduced in 2009 as commissioned by the Department of Health [94]. PROMS data were given further impetus within the NHS in 2010 through the White Paper document 'Equity and Excellence: Liberating the NHS', which placed an emphasis on shared decision-making between patients and clinicians, with PROMS data being central to this process [95].

The political emphasis on PROMS data combined with a desire to improve patient outcomes has led to a fundamental shift in the measurement of outputs within the NHS, extending traditional outputs of clinically defined variables to include the patient perspective through the routine collection of PROMS data. Initially, piloted in four elective surgical procedures, to include hip and knee replacement, hernia surgery and varicose vein surgery, there are plans underway to expand the NHS PROMS programme to include a number of chronic diseases and selected cancers including colorectal cancer.

The publication and dissemination of routinely collected mandatory standardised PROMS data within the NHS has a number of advantages and can help inform patients, clinicians and health-care commissioners when evaluating the quality and equity of current healthcare services. From a patient perspective, PROMS data can help guide patients to appropriately identify their care provider under the remit of the 2008 NHS initiative of open choice [96-100], with clinician-level PROMS data further contributing to this choice of service provider. There is emerging evidence from the dataset collected through the PROMS programme for elective orthopaedic procedures that this data may be a more sensitive indicator of consultant outcomes when compared to elective post-operative mortality [101]. Furthermore, PROMS data can provide supplementary information to clinical outcomes when guiding patients with regards to treatment options [102, 103], with this being of the most importance

when considering treatments where the survival benefit is modest or symptom control is the primary outcome [104-106].

Using PROMS to inform and guide clinical decision-making provides clinicians with a broader perspective on patients overall health status. PROMS can be used to screen diseases, monitor response to treatments, evaluate disease progression/regression by comparing baseline PROMS data to serial measurements, highlight unique issues engendered by treatments and improves communication between patients and health-care providers [107, 108].

The recent landmark Montgomery ruling will potentially impact on the way in which PROMS will be used to help inform and guide clinical decision making when informing and consenting patients regarding potential treatment options. The new ruling requires healthcare professionals to consider whether "a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to" [109]. This ruling emphasises the individual nature of the consent process, focussing on patient autonomy and emphasising the importance of patient centred approach. When considering major surgery patients value PROMS data including QoL over other aspects of care [110] [111]. In view of patients needs to be informed about HrQoL data in combination with the Montgomery ruling makes it an opportune time to integrate PROMs data with clinical and oncological data, and present this data in tandem when discussing treatment options with patients.

From a health care commissioning perspective PROMS can provide a unique and insightful perspective into the delivery and outputs of health services. PROMS can be used to monitor performance from healthcare providers, incentivise providers to improve patient health by linking payment to performance in PROMS, benchmark performance of different healthcare providers using PROMS data and may be helpful in identifying inequitable variations in patient health outcomes [112, 113]. Furthermore, PROMS data can be used to assess cost-effectiveness by combining this data with provider-level costs to quantify the health gain and associated costs for interventions [113]. Employing this approach with data from the NHS PROMS Programme cost-effectiveness has been determined for elective laparoscopic inguinal hernia repair [114] and elective hip replacements [115].

PROMS measurement within the NHS has great potential to enhance patient experience and outcome, guide clinical decision-making, benchmark performance and influence policy. The initial success of the NHS PROMS Programme and its subsequent plans for expansion suggests PROMS are a valuable and credible source of information in the quest for improving patient outcomes at a local and national level.

1.3.2 PROMS Measurement in Clinical Research

There is a steady movement towards measuring PROMS in clinical research, most notably within the remit of randomised clinical trials [116-118]. Oncology trials most commonly employ PROMS data to examine differences between treatment arms [118-121]. QoL and PRO outcomes are of increasing importance in advanced and palliative oncology trials where large survival benefits are unlikely to be realised. Randomised controlled trials represent the gold standard of treatment efficacy, representing Level I evidence for guiding evidence-based medicine. Therefore, the increased use of PROMS data in clinical trials has the potential to provide high quality data to guide patients and clinicians, by providing scientific rigour necessary for valid outcome interpretation. This has been recognised and encouraged by a number of international bodies including The Radiation Therapy Oncology Group [122], National Cancer Institute Clinical Trials Cooperative [123, 124], The US Food and Drug Agency [125] and the European Organisation for Research and Treatment of Cancer [126].

Alongside measuring PROMS in clinical trials there is much work being dedicated to using population-based registries in collecting this data [127-131], which would be ideally placed for the measuring of PROMS outcomes in LRRC. Using population-based cancer registries to document PROs is associated with a number of advantages including a large sample size, high external validity, ability to compare the clinical demographics of responders and non-responders, explore PROs in rare cancers and monitoring changes to PRO data before and after diagnosis [132]. In current practice, these registries are being used as sampling frameworks to assess PROs in long-term cancer survivors, thus providing a cross-sectional, ‘snap-shot’ perspective of outcome [127]. These disease registries have already been established to measure clinical outcomes, with the measurement of PROs being a

secondary endpoint once the registry is successfully established. This has important implications on the results obtained with variable response rates, lack of baseline data and potentially important differences between responders and non-responders missed. However, despite these shortcomings the use of population based registries has the potential to amass a large wealth of PRO data alongside clinical data over a relatively short period of time whilst reflecting the needs of the population and enabling comparisons between different service providers. To be successful in collecting PROMs data within the framework of a registry consensus is required from all key stakeholders, including patients and clinicians, on the type of PROM included, its linkage with registry data, standardisation of data collection and on-going evaluation of data collection to improve compliance [133].

Given this rise in the inclusion of PROMS data in clinical trials and population registries, there has been much work targeted at standardising the reporting of PROMS outcome data, specifically HrQoL [134]. Current practice of reporting PROMS in clinical trials is highly variable with regards to the quality of data analysis and reporting [135-138]. This variation in reporting of PROMS outcome data produces inconsistencies in data interpretation and therefore potentially leads to the lack of application of this data to clinical practice. To improve the scientific rigour of reporting HrQoL data in oncology trials a minimum set of criteria was proposed as a checklist in 2003 [139]. Using this checklist as guide a higher proportion of methodologically robust randomised controlled trials reporting HrQoL were identified following the guidelines inception [140]. However, despite these recommendations, the reporting of PROMS within the context of clinical trials remains suboptimal, with Brundage et al reporting the failure to report on the rationale for inclusion of PROM, on HrQoL hypothesis, missing data and appropriate sample size in 794 randomised controlled trials across a range of clinical conditions [135]. Furthermore, this review identified inconsistencies in data reporting and presentation. These systematic errors in trials incorporating and reporting on PROMS data are due to insufficient detail included in the trial protocols, with inadequate detail provided on relevant existing PRO research, a rationale of collecting PRO data, provision of a PRO specific hypothesis, justification of PROM timings, PRO sample size calculations, justification of PROM used, lack of data on the clinical significance of PRO data, lack of detail on handling of missing data and PROM

specific data monitoring [141]. The acknowledgement of these inadequacies in current reporting methods of PROMS data within the context of clinical trials has led to the extension of the Consolidated Standards of Reporting Trials (CONSORT) to include PROs as the CONSORT-PRO. This guideline aims to improve the methodological rigour of assessing and reporting PROMS data, by making five key recommendations which include:

1. that PROs are identified as a primary or secondary outcome in the abstract,
2. that a description of the hypothesis and relevant domains be provided (if a multidimensional PRO tool has been used),
3. that evidence of instrument validity and reliability be provided or cited,
4. that the statistical approaches for dealing with missing data be explicitly stated,
5. that PRO-specific limitations of study findings and generalizability of results to other populations and clinical practice to be discussed.

To ensure the continued use of PROMS to identify key differences between treatments in clinical research requires complete transparency and disclosure of results. Adopting a robust, methodological approach under the guidance of the CONSORT-PRO statement will allow for accurate and valid PROs to be obtained through well-designed research studies [142]. This will enable clinicians to critically appraise PROMS data prior to utilising this data to inform clinical decision-making.

1.3.3 PROMS Measurement in Colorectal Surgery

There is a strong heritage of PROs across the speciality of colorectal surgery, given its sensitive and personal nature, combined with its reliance on the subjective reporting of symptoms to aid diagnosis and treatment. Generic and disease-specific measures are available to assess PROs in all subspecialty areas of colorectal surgery including colorectal cancer [143-145], inflammatory bowel disease [146], pelvic floor disorders [147, 148] and functional bowel disease [149, 150]. There has been an acknowledgement in recent times by the colorectal fraternity of the role played by PROMS in clinical

practice, audit and research. With this there has been a concomitant rise in the use of PROMS in clinical colorectal trials and comparative effectiveness research [151-162], with an increasing number of studies using PROMS as the primary endpoint [161, 163-166], thus providing a patient-centred approach to evidence-based medicine in this field of surgery. However, despite, this increase in the use of PROMS in colorectal research the standard of reporting PROMS data remains suboptimal with only a third of colorectal cancer trials reporting high quality PROMS data [136]. The underreporting of good quality, robust PROMS data detracts from its importance and application in the clinical setting and therefore prevents its use in clinical practice.

A range of disease-specific measures currently exist for measuring PROMS outcomes in colorectal disease, which reflects the steady movement away from the use of generic PROMS in evaluating HRQoL outcomes in patients with specific diseases[167]. Disease-specific measures have the ability to detect and evaluate subtle changes between patient and treatment groups, which may potentially be missed by generic measures [168-171]. It is therefore essential to use validated, disease- specific measures to produce clinically meaningful and relevant data [172]. A number of disease-specific PROMS have been developed and validated for use in colorectal cancer [143, 144], these measures have been found to be more sensitive and responsive in detecting clinical changes when compared to generic measures [171]. Building on from this there has been much work in developing validated PROMS in patients with metastatic colorectal cancer, most notably, in those with liver metastases [173, 174]. The development of a disease-specific measure for patients with colorectal liver metastases acknowledges this cohort of patients have a unique set of issues which differ from patients with primary colorectal cancer [174]. It can be hypothesised the same principles apply to patients with LRRC, with these patients being affected by a unique set of issues, which may not be captured by existing PROMS developed for use in primary colorectal cancer. Just as patients with colorectal liver metastases have been defined as a clinically significant group with a dedicated PROM, it is important we acknowledge the LRRC group in a similar fashion. This is further justified by the differences observed in clinical outcomes between primary advanced rectal and recurrent rectal cancer, with a higher proportion of curative resections and prolonged survival in the locally advanced

group compared to the recurrent group [17, 175-177]. Whilst traditional clinical outcomes have been examined between these two clinically distinct groups, HrQoL and PRO outcomes have only been examined in the primary rectal cohort using validated PRO measures [178-180]. Acknowledging these differences in clinical outcomes between primary rectal cancer and recurrent rectal cancer further reinforces the hypothesis that similar differences may exist between these two groups with regards to HrQoL. This is an opportune time to examine and develop a disease-specific PROM in patients with LRRC with endorsement from two international collaboratives [6, 7].

1.4 Conclusion

LRRC is a complex disease entity, with a number of treatment options available. The surgical and oncological outcomes associated with LRRC are well documented, however, little is known about the impact of LRRC and its treatments on HrQoL. There is growing interest within the surgical fraternity in documenting these important outcomes in patients with LRRC and integrating these outcomes with traditional clinical and oncological outcomes, in a bid to provide a more balanced perspective. The current landscape for PROMS measurement is changing, with recognition and endorsement from a number of key stakeholders including politicians, policy-makers and clinicians. PROMS data can be used for a variety of reasons including service improvement, national benchmarking, clinical monitoring and decision-making. This is reflected in the upward trend of including PROMS data in clinical trials and population registries and the increasing guidance available on the incorporation of PROMS in such studies. There is a paradigm shift in surgical oncology with a focus on integrating clinical and patient-reported outcomes. This makes it an opportune time to acknowledge the complexities of managing patients with LRRC, to employ a patient-centric approach and investigate HRQoL in this cohort.

2 Chapter 2 - Systematic Review of Health-Related Quality of Life in Locally Recurrent Rectal Cancer

2.1 Background

Traditionally, surgical endpoints, such as morbidity, mortality and overall survival are used as markers of success of an operative intervention. In the complex scenario of LRRC operative intervention is not always performed with curative intent, but to palliate symptoms and improve HrQoL. There is a steady movement away from the traditionally paternalistic model of healthcare delivery, with a greater emphasis on PROs, which include HrQoL [88]. Such outcome measures are gaining increasing momentum in assessing efficacy of new treatments and the effectiveness of existing treatments as well as obtaining information on patient perceived benefits and risks of treatments. There has much been much interest in PROs, namely HrQoL outcomes in patients with LRRC in recent times [181]. It is believed that assessment of HrQoL of patients with LRRC may help inform the current on going debate of the management of this cohort of patients, especially with regards to further radicalisation of curative surgery and palliative surgery and the cost-effectiveness of these interventions.

2.2 Aims

The aims of this review were:

- to identify and assess the current literature on HrQoL outcomes in LRRC
- to identify tools used to assess HrQoL in patients with LRRC
- to identify common HrQoL themes in patients with LRRC.

2.3 Methodology

2.3.1 Search Strategy

Literature searches were performed in three databases: MEDLINE (1966-January 2013), EMBASE and CINAHL. The searches were limited to the English language. The major subject heading, LRRC, was combined with HrQoL, QoL, symptom control, questionnaires, physical distress, psychological distress and psychosocial distress. The search was designed to identify qualitative research that explored patients' subjective experience and quantitative studies that measured HrQoL using standardised measures.

To identify on going and unpublished research, hand searches of specialist journals and relevant conference proceedings were carried out. An Internet search of web content relating to LRRC self-help and focus group websites was also undertaken (Appendix 1).

2.3.2 Study Inclusion Criteria

Studies were included if they fulfilled the following criteria; they reported outcomes of patients with LRRC, including symptom control, HrQoL outcomes and impact on function. Patients undergoing surgery and palliative treatments were included. Studies were excluded if LRRC HrQoL outcomes were not measured. Case reports, reviews and letters were excluded.

2.3.3 Selection of Studies

Abstracts from studies retrieved were screened for relevance; studies that did not meet inclusion criteria at this stage were excluded at this stage. Studies assessed as potentially relevant, or where relevance was ambiguous, were obtained in full, for further scrutiny.

2.3.4 Data Extraction

Data extraction was conducted independently by two reviewers (Deena Harji, DH and Ben Griffiths, BG). The following information was extracted from each study; first author, year of publication, study population characteristics, study design (prospective, retrospective, or other), number of patients in each group (total number of patients assessed and number of patients with LRRC), comparative groups, HrQoL assessment tool used, median time interval between diagnosis/treatment and assessment, main findings and quality of study.

2.3.5 Data Quality

The methodological issues surrounding the quality of the studies assessing and measuring HrQoL in LRRC were considered A pragmatic approach was undertaken to include all studies reporting HrQoL outcomes and patient testimony irrespective of the quality of the study, due to the sparsely available literature on this topic. However, a quality analysis was undertaken of all published studies included in accordance with the Newcastle-Ottawa Scale (NOS) for assessment of non-randomised studies[182]. There are two separate scoring systems incorporated into the NOS dependent on study type; case-control study or cohort study. There are three general areas in which each study is marked, which includes selection, comparability and exposure for case-control studies and outcome in cohort studies. Studies are marked against pre-defined criteria using a star system, with a maximum of 10 stars available for case-control studies and 13 stars for cohort studies. Studies were deemed as good quality if a minimum of 7 stars are scored.

2.3.6 Data Analysis

All studies were evaluated for the following criteria; a definition of HrQoL, use of a valid and reliable instrument, compliance issues, handling of missing HrQoL data, reporting of statistical methods employed, examination of clinical significance and reporting in detail the presentation of results.

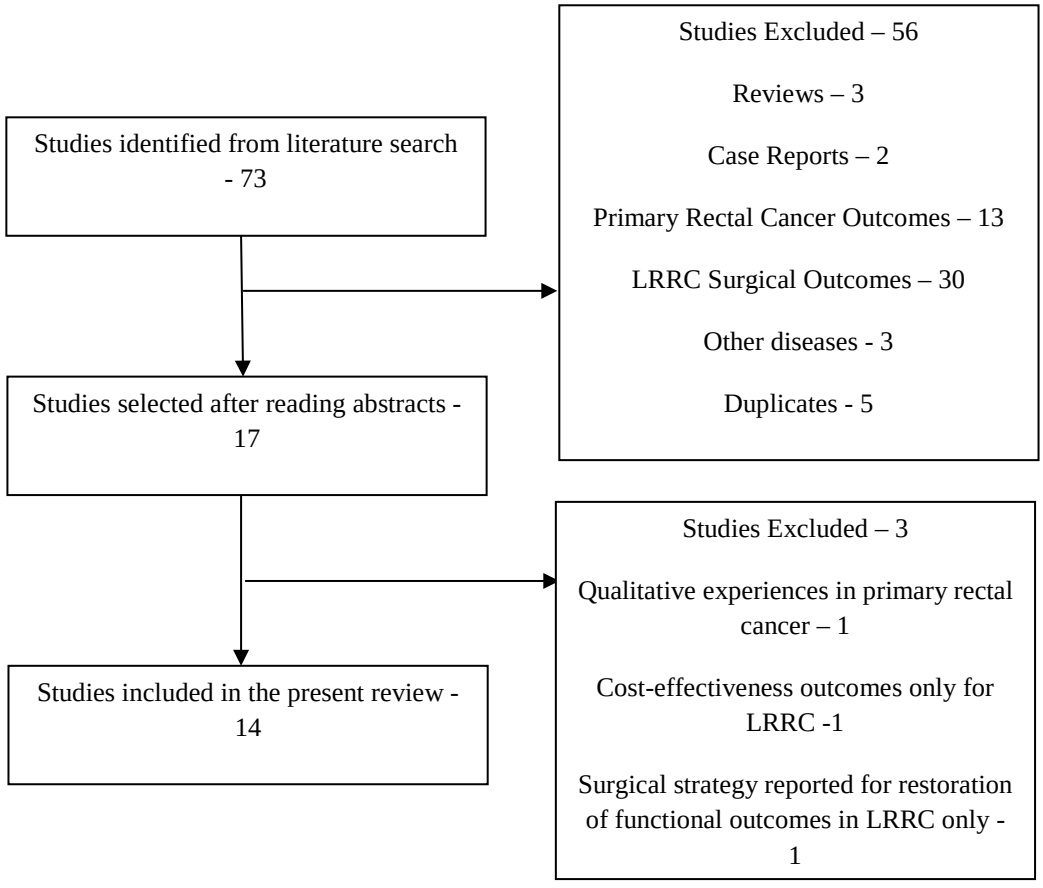
A combined synthesis of qualitative and quantitative research was performed. This process involved the generation of a priori distribution of factors and their relative importance using the principles of content analysis to generate common categories and themes from the study findings. The principles of triangulation for integrating mixed methods data were used to determining consistency between findings from each data set [183] [184]. A meta-synthesis of the qualitative data was carried out, with all relevant findings grouped together. Common categories and themes were identified from the study findings. A category was determined by grouping similar findings reflecting similar underlying constructs. In turn categories were synthesised into themes, if they were sufficiently similar, this enabled the summary of all evidence for a particular domain. The same process was carried out for the quantitative data, with findings from the quantitative data set encoded to the categories identified from the meta-synthesis if appropriate, or to new categories. This process enabled comparison between findings from the two types of data sets (qualitative and quantitative), thus enabling the review of all emerging categories and assessing for consistency, discrepancy and complementarity between two the data sets. The combined categories and themes were reviewed and synthesised into a working conceptual framework for HrQoL specific LRRC.

2.4 Results

The search strategy identified a total of 73 references. Five duplicates and 51 inappropriate references were identified through examining the abstracts and were excluded (Figure 2.1). The remaining 17 abstracts were retrieved for further evaluation, of which 14 were included in this review. This identified a total of 946 patients with locally advanced rectal cancer (LARC), LRRC and recurrent

gynaecological malignancy, of which 501 (52.9%) patients had LRRC. A total of 676 (71.4%) patients completed the full complement of assessment tools, with assessments carried out at a median age of 64. This included 330 (48.8%) male and 278 (41.1%) female patients. The gender is unknown in 68 (10.1%) patients. Operative intervention, curative or palliative, was the commonest mode of treatment, with 403 (80.4%) of patients with LRRC undergoing surgery alone or in combination with chemotherapy +/- radiotherapy. Forty-five (8.9%) patients underwent palliative chemotherapy +/- radiotherapy or best supportive treatment for LRRC. The treatment modality is unclear in 53 (10.5%) patients with LRRC.

Figure 2-1 Flowchart of Studies Retrieved From Literature Search



Twelve published studies [27, 185-195] and two abstracts[196, 197] were identified, of which 12 studies were quantitative, 1 qualitative study and 1 study employed mixed methodology, reporting

qualitative and quantitative data. No randomised controlled trials were identified. The number of patients with LRRC participating in each study ranged from 2-105. Study design included 5 retrospective cohort studies, 3 retrospective case control studies, 4 prospective longitudinal studies, 1 prospective cross-sectional study and 1 qualitative interview. A summary of the main points of each study is highlighted in Table 2.1, with quality analysis of all studies outlined in Table 2.2. The quality of the studies included were generally poor according to the NOS scoring system, with only one high scoring study included (Table 2.2). A total of 28 patient forums were identified on LRRC from three public cancer websites, including Beating Bowel Cancer, Macmillan and Cancer Research UK. These patient forums were analysed to identify relevant patient testimony.

Table 2-1 Summary Findings of the Studies Included Outlining HrQoL in LRRC

Author and Year	Study Population	Study Design	Total No Patients	Total No of Patients with LRRC	Comparative Group	Treatment of Patients	Median Time Interval Between Diagnosis/Treatment and Assessment	Number of Assessments	HrQoL Assessment Tool	Main Findings
Camilleri-Brennan[185] 2001	LRRC and DM*	Retrospective Cohort Study	25	13	Age and sex matched disease free patients	-	24 months	1	EORTC QLQ-C30/QLQ-CR38 SF36 II	QoL scores were lower in patients with tumour recurrence compared to matched controls with no recurrence.
Guren [193] 2001	LRRC and LARC	Retrospective Case-control cross-sectional study	12	2	Patients with LRRC/LARC without urinary diversion and reference Norwegian population	Surgery and RT^{+} - 2	-	1	EORTC QLQ-CR38 EORTC QLQ-BLM30	Comparable QoL scores between patients with and without urinary diversion.
Mannaerts [189] 2001	LRRC and LARC	Retrospective Cohort Cross-sectional study	76	39	LARC patients	Surgery, RT and $IORT^{++}$ – 39	14 months	1	Symptom scales	Significant post-operative urogenital dysfunction in both LARC and LRRC, with higher rates observed in the female population.
Esnaola [188] 2002	LRRC	Prospective Longitudinal Study	45	45	LRRC patients treated with non-surgical palliation	Surgery - 9 Palliative alone -8 Surgery and CRT^{+++} - 3 Surgery, CRT and IORT - 10	1 month*** or 15.2 months****	3 monthly	BPI FACT-C	Worse pain scores in patients undergoing non-surgical palliation compared to those undergoing curative surgery. Pain affected QoL. QoL is impaired initially for patients undergoing surgery however returns to baseline within 3 years.

						Surgery and CT - 4 Palliative CRT - 8 Supportive Care - 3				
Mannaerts [190] **2002**	LRRC and LARC	Retrospective cohort cross-sectional study	76	39	LARC patients	Surgery, RT and IORT – 39	14 months	2	Symptoms scales	LRRC patients had a higher degree of post-operative morbidity, social handicap and functional impairment when compared to LARC.
Miner [27] **2002**	LRRC	Retrospective Cohort Study	105	105	LRRC treated with surgical palliation	Curative surgery - 81 Palliative Surgery - 24	-	2	Symptom scales	Clinical improvement was observed in 42% of patients following palliative surgery and in 78% of patients undergoing non-palliative surgery.
Wright [194] **2006**	LRRC and LARC	Qualitative Interview	10	3	None	Surgery and RT - 1 Surgery and CRT -7 Surgery and CT - 1	11 months	1	Qualitative Face to Face Interview	Patient experiences reflected a highly focused desire to seek cure, however revealed a misunderstanding of disease biology, probability of cure, therapeutic options and treatment morbidity.
Palmer [192] **2008**	LRRC, LARC and LASC**	Retrospective Case-control cross-sectional study	43	13	Age-sex matched patients with operable primary rectal cancer and reference Swedish	Surgery - 43	9-149 months	1	EORTC QLQ-C30/QLQ-CR38	Lower global, physical, role, social functioning and body image scores in the study group. No differences were observed in colorectal cancer symptoms between the two groups.

					population					
Austin [191] **2010**	LRRC and LARC	Retrospective case-control cross-sectional study	37	20	Primary rectal cancer patients and reference Australian population	Surgery - 20	47 months	1	FACT-C SF36 II	Comparable QoL scores between study group and primary rectal cancer patients.
Zoucas [186] **2010**	LRRC/LARC/ Gynaecological malignancy	Prospective Longitudinal study	85	20	None	-	4 and 16 months	2	EORTC QLQ-C30	HrQoL improved at 16 months post-operatively.
You [187] **2011**	LRRC	Prospective Longitudinal study	105	105	LRRC treated with non-curative surgery and non-surgical palliation.	Curative surgery - 12 Curative surgery and CRT - 50 Non-curative surgery - 13 Palliative CRT - 21 Palliative brachytherapy - 2 Supportive treatment - 7	-	3 monthly	FACT-C BPI	Physical well-being was better in patients undergoing curative surgery compared to non-curative or non-surgical treatments. QoL scores were largely preserved in all three groups.
Vaughan [198] **2012**	LRRC and LARC	Prospective cross-sectional study	45	20	-	-	-	1	EORTC QLQ-CR30 EORTC QLQ-CR29	Global health status and pain were better in patients undergoing surgery compared to non-surgical palliation ($p<0.001$). Greater buttock

										pain was the only difference between LRRC and LARC patients.
Thaysen [196] **2012**	LRRC and LARC	Prospective Longitudinal Study	126	59	Primary rectal cancer patients and reference Danish population	-	-	4	EORTC QLQ-C30 EORTC QLQ-CR29 SF36 II	No differences were found in HrQoL compared to patients with primary rectal cancer. Global quality of life was comparable to the general population. Clinically significant lower HrQoL was found in relation to role function, bodily pain and emotional role.
Holman [195] **2013**	LRRC and LARC	Retrospective Cohort Cross-sectional Study	51	18	LARC patients	Surgery and CRT – 49 Surgery – 2 Additional IORT -44	3 years	1	EORTC QLQ-C30 EORTC QLQ-CR38 Qualitative Interview	After vaginal reconstruction, women reported equal or higher scores on global health status, emotional functioning and body image. Following reconstruction, 40% of women were unable to engage in sexual intercourse due to technical reasons.

* DM = distant metastases, ** LASC – Locally advanced sigmoid cancer, + RT – Radiotherapy, ++ IORT – Intraoperative radiotherapy, +++ CRT – Chemoradiation, ^CT – Chemotherapy ***Non-surgical palliation only ****Surgical treatment

Table 2-2 Quality Assessment of All Published Studies Included According to the Newcastle-Ottawa Scale

CASE-CONTROL STUDIES				
	SELECTION	**COMPARABILITY**	**EXPOSURE**	**OVERALL SCORE**
Guren [193]	***	*	*	5
Palmer [192]	***	-	*	4
Austin [191]	***	**	**	7
COHORT STUDIES				
	SELECTION	**COMPARABILITY**	**OUTCOME**	**OVERALL SCORE**
Camilleri-Brennan [185]	**	**	-	4
Mannaerts [189]	*	**	**	5
Esnaola [188]	**	*	**	5
Mannaerts [190]	*	**	**	5
Miner [27]	**	**	**	6
Zoucas [186]	**	*	**	5
You [187]	**	*	**	5
Holman[195]	**	-	**	4

Table 2.3 highlights the methodological and statistical design issues associated with each identified study. HrQoL was the main primary endpoint in 9 studies[185, 187, 188, 191, 192, 194, 196, 197], with clinically significant differences determined prior to study commencement in 7 studies. Compliance with completion of HrQoL assessments were reported by 12 studies, with reported compliance ranging from 60-100%. Baseline assessments of HrQoL prior to the initiation of treatment were available in five studies alone [27, 187-190], with the majority of assessments being carried out at a median time frame of 4-149 months following diagnosis and/or treatment of LRRC [186, 189-192, 194, 195]. Handling of missing data was reported by 3 studies alone [188-190].

Table 2-3 Statistical and Design Issues Assessing HrQoL in LRRC

Author	Definition of HrQoL	Primary Outcome	Use of Valid and Reliable Instrument for LRRC	Compliance	Handling of Missing Data	Baseline Characteristics Reported	Method of Analysis Reported	Follow-Up Data Reported	HrQoL significance addressed	HrQoL significant
Camilleri- Brennan[185]	No	HrQoL	No	83%	Not reported	No	Yes	Yes	Yes	Yes
Zoucas [186]	No	Clinical	No	Not reported	Not reported	No	Yes	Yes	Yes	Yes
You [187]	No	HrQoL	No	Not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Esnaola [188]	No	HrQoL	No	88%	Yes	Yes	Yes	Yes	No	Yes
Mannaerts [189]	No	Clinical	No	96%	Yes	Yes	Yes	Yes	No	Yes
Mannaerts [190]	No	Functional Outcome	No	96%	Yes	Yes	Yes	Yes	No	Yes
Austin [191]	No	HrQoL	No	84%	Not reported	No	Yes	N/A	Yes	No
Palmer [192]	Yes	HrQoL	No	89%	Not reported	No	Yes	N/A	Yes	Yes
Guren [193]	No	HrQoL	No	97%	Not reported	No	Yes	Yes	Yes	Limited
Wright [194]	No	HrQoL	Qualitative Interview	100%	N/A	N/A	Yes	N/A	No	No
Miner [27]	No	Clinical	No	60%	Not reported	Yes	Yes	Yes	No	No
Holman [195]	No	Clinical and HrQoL	No	85%	Not reported	No	Yes	Yes	Yes	Yes
Thaysen [196]	No	HrQoL	No	74%	Not reported	No	No	Yes	No	Yes
Vaughan-Shaw [198]	No	HrQoL	No	91%	Not reported	No	No	Yes	No	No

2.4.1 HrQoL Assessment Tools

Nine studies utilised HrQoL tools used to assess outcomes in primary rectal cancer, this included the Functional Assessment of Cancer Therapy-Colorectal Specific Questionnaire (FACT-C) [187, 188, 191], European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [186] combined with the colorectal specific modules EORTC QLQ-CR38 [185, 192, 193, 195] and EORTC QLQ-CR29 [196, 197]. Five studies incorporated the Short-Form 36 Version II (SF36-II) [185, 191, 196] and/or the Brief Pain Inventory [187, 188, 199] to assess generic outcomes. One study used the European Organisation for Research and Treatment of Cancer Bladder Cancer questionnaire (EORTC QLQ-BLM30) [193]. Three studies utilised ad hoc symptom scales, specifically designed for the individual study [27, 189, 190]. No disease-specific tools were identified to measure HrQoL outcomes in LRRC.

2.4.2 Identified HrQoL Themes

Using the principles of content analysis one hundred and eighty four findings, thirty categories and eight themes were identified (Table 2.4).

Table 2-4 Synthesised Categories and Themes Identified

Theme	Category
Physical impact	Physical restrictions due to LRRC symptoms and treatment interventions Adaptation of physical environment to facilitate impact of LRRC
Psychological impact	Impact on mental health and psychological well being Employment of coping mechanisms Future perspective

	Anxiety Anger Acceptance and health bargaining
Social Impact	Social life restricted due to physical restrictions Adaptation of social circumstances to facilitate impact of LRRC Affect on personal life and relationships
Symptoms	General Health Stoma issues Gastrointestinal Symptoms Genitourinary Symptoms Musculoskeletal Symptoms Pain Descriptors
Financial Impact	Financial Difficulties Delayed Return to Work Change of occupation to accommodate restrictions imposed by LRRC
Relationships With Others	Paternalistic relationship with healthcare professionals Dependence on others
Communication	Need for information Delay between referral from GP to specialist services Difficulty seeking second opinions Frustration regarding miscommunication and delayed communication between specialist services and primary consultant Misunderstanding of disease biology and treatment options due to lack of communication
Sexual Function	Emotional aspects of sex Technical aspects of engaging in sexual activities Sexual enjoyment

2.4.2.1 Physical Impact

Physical function is defined as the 'ability to carry out various activities that require physical capability, ranging from self-care, including basic activities of daily living, to more vigorous activities that require increasing degrees of mobility, strength or endurance'.

Eleven studies reported the impact of LRRC on physical well being and functional outcomes with conflicting outcomes [185-188, 190-192, 194-197]. Camilleri-Brennan et al reported lower scores of physical well being using the EORTC QLQ-CR38 in patients with locoregional recurrence compared to disease free patients [185]. Conversely, Austin et al failed to detect any clinically significant differences in physical well being scores using the FACT-C between patients undergoing surgery for LARC or LRRC cancer requiring extended resection compared to primary rectal cancer [191], unlike Palmer et al who reported lower physical functioning scores on the EORTC QLQ-CR38 in LRRC and LARC patients when compared with a similar comparative group [192]. You et al reported lower physical well being scores using the FACT-C questionnaire combined with higher scores of pain interference with activities of daily living in patients undergoing non-curative surgery compared to patients undergoing curative surgery [187].

Mannaerts et al reported the functional impact on patients undergoing surgery for LRRC, with patients experiencing post-operative walking difficulties and requiring help with basic activities [190]. Wright et al reported patient experiences following surgery for LARC or LRRC with patients reporting adverse effects on mobility, activities of daily living and leisure activities [194].

Two longitudinal studies from the same unit, both reported long term return of physical functioning to baseline levels in the patients treated surgically with curative intent at 3 and 7 years respectively [187, 188], However, in the non-curative patients treated surgically and in the palliatively treated patients, physical functioning scores deteriorated with time [187].

2.4.2.2 Psychological Impact

Psychological impact is defined as the impact on one's mental and emotional well being. Seven studies commented on psychological impact following surgery for LRRC [185, 187, 188, 191, 193-195] using the emotional well being and emotional function domains of the FACT-C and the EORTC QLQ-C30 questionnaires respectively.

Patients undergo a range of emotions during the diagnosis and treatment of LRRC, according to the qualitative experiences reported by Wright et al [194], these range from desperation, despair and helplessness when seeking a diagnosis of LRRC followed by a more motivated outlook during the post-operative recovery period, due to the employment of coping mechanisms and health-bargaining. The psychological impact of LRRC has a considerable effect on the future perspectives on this cohort of patients, however this is partially dependent on the experience during the management of the LRRC, as Camilleri-Brennan reported lower scores of future perspective in patients with LRRC [185]. However, Palmer et al reported equivalent scores between patients with LRRC/LARC and patients with primary rectal cancer [192]. Similarly, Austin et al reported higher mental well being scores in patients undergoing exentarative surgery for LARC/LRRC compared to the general Australian population despite having lower physical well being scores [191].

Patient experiences reported on internet cancer support forums suggest a great deal of anxiety in the initial diagnostic and investigative phases of LRRC treatment, with occasional anger expressed at the prospect of disease recurrence and the 'failure' of primary treatment. Once the diagnosis and treatment pathway is established, a more positive and accepting attitude is adopted.

2.4.2.3 Social Impact

Social function is defined as the ability of one to participate and engage in social and recreational activities. LRRC had an impact on social functioning as reported by five studies [185, 190, 193, 194]. The impact on social function was assessed using qualitative interviews [194] or through quantitative

measures including EORTC QLQ-C30 [185, 193], EORTC QLQ CR38 [185, 193] and ad hoc questionnaires designed specifically for the study [190]. Camilleri-Brennan reported a greater impact on role functioning in patients with LRRC compared to disease-free patients [185]. The negative impact on social functioning is multifactorial with contributing factors including invasive diagnostic investigations, pre-operative treatments including chemoradiation and the operative burden with its high associated morbidity rate. Interestingly, the resumption of normal social activities is described to be a motivating factor to get better by patients [194].

2.4.2.4 Symptoms

Given the heterogeneous nature of LRRC with its variable disease pattern and the range of operative interventions available, patients present with and experience a multitude of symptoms affecting a range of systems, including the gastrointestinal, genitourinary and musculoskeletal systems. Such symptoms are a source of anxiety for patients in the pre-operative and post-operative periods. Furthermore, symptoms can be attributable to a number of factors including post-operative complications and disease re-recurrence. A total of 9 studies commented on a variety of symptoms in patients with LRRC, with pain and gastrointestinal symptoms being the most commonly reported [27, 185, 187, 188, 190, 193-195, 197].

- **Pain**

  Pain is a common presenting symptom in patients with LRRC, with this being the chief complaint in up to 40% of patients [27]. Pain is typically described to be pelvic, perineal or sciatic in nature. Mannaerts et al used an adhoc scale to report differences in post-operative pain based on initial subsite of pain, with worsening post-operative pain scores [190]. Esnaola et al reported the presence of pelvic or sciatic pain at presentation was a strong predictor of poor overall outcome [188].

Two studies used the generic pain scale, the Brief Pain Inventory [199] to assess pain in this cohort of patients. You et al observed no differences in pain scores between patients treated curatively or palliatively over the length of their study [187]. However, this group demonstrated the prognostic significance of pain on overall survival, with patients reporting a pre-treatment pain intensity score of less than 4 surviving for a median of 3.8 years compared to 2 years in patients with scores of more than 4 (p=0.001). Conversely, Esnaola et al observed worsening pain scores in patients treated with non-surgical palliation over a 3 year period compared to those treated surgically, with median pain scores of 8 and 3 at 12 months (p=0.2), with long term survivors (> 3 years) of surgical resection reporting a median pain score of 0 [188]. Pain had a significant impact on QoL, with patients with low pain scores reporting better QOL scores compared to those with higher pain scores (p=0.001).

- ***Gastrointestinal symptoms***

  As expected patients with LRRC experience a greater degree of gastrointestinal (GI) symptoms compared to disease-free patients [185]. However, patients undergoing surgery for LRRC experience a considerable number of GI symptoms in the post-operative period related to incontinence and stoma-related problems, Mannaerts et al observed a 25% higher post-operative complaint rate in patients with LRRC compared to LARC [190].

- **Genitourinary symptoms**

  Given the anatomical proximity of the neural plexus supplying the urogenital organs and the potential of disease invasion of these organs, a significant proportion of patients with LRRC will have a degree of urogenital dysfunction. This can be as a consequence of the primary surgery, radiotherapy, disease recurrence or recurrent surgery itself. Mannaerts et al reported significant post-operative urinary and sexual dysfunction in patients treated in a multimodal fashion (radiotherapy, surgery and intra-operative radiotherapy) for both LARC and LRRC, with these differences most pronounced in the female sex [189]. According to this group of authors, 56% of

patients with LRRC reported post-operative voiding dysfunction compared to 22% pre-operatively (p=0.001).

A proportion of patients will need a total pelvic exenteration to achieve complete disease clearance, leaving them with two stomas, typically a colostomy and a urostomy. Guren et al compared QoL outcomes between patients requiring urinary diversion in the form of a urostomy and those who had the urogenital system preserved, with no significant differences observed between the two groups and the reference group, which consisted of the Norwegian general population [193].

- **Musculoskeletal Symptoms**

  The commonest musculoskeletal complaint in patients with LRRC is mainly that of lower limb weakness and pain leading onto subsequent difficulties with mobility. Mannaerts et al reported post-operative lower limb pain in 42% of patients compared to 21% pre-operatively, with 56% complaining of reduced lower limb strength in the post-operative period compared to 13% in the pre-operative phase, and walking difficulties reported by over half of all patients with LRRC [190]. Wright et al reported the qualitative comments of two patients, one of whom complained of intermittent foot swelling and difficulties walking and the second who complained of no lower limb control [194].

2.4.2.5 Financial and Occupational Impact

Impact upon financial and occupational status is defined as a change in economic status due to a change in the financial and occupational status following treatment of LRRC. This was commented upon in 3 studies through the use of the EORTC QLQ C30, EORTC QLQ CR38 and ad hoc questionnaires [185, 190, 193].

Guren et al reported higher scores of financial difficulty in patients undergoing surgery for LRRC and LARC with urinary diversion compared to patients without urinary diversion [193]. A similar observation was reported in patients with LRRC compared to disease-free patients following treatment of primary rectal cancer [185].

Undergoing treatment for LRRC has significant impact upon occupational recovery. Mannaerts et al reported 50% of patients returned back to their former lifestyle following surgery for LRRC, with 18% of patients returning to their former occupation and a further 13% of patients returning to lighter occupational duties [190].

2.4.2.6 Relationships with others

An impact on relationships was defined as a change in the role and interactions in personal and professional relationships. This was commented on in two studies using the EORTC QLQ-BM30 questionnaire and through the use of semi-structured qualitative interviews [192-194].

Post-operatively, patients with urinary diversion for LRRC and LARC reported a greater dependence on others with regards to urostomy care and urostomy-related problems [193]. Wright et al, reported on the qualitative experiences of patients undergoing surgery for LARC or LRRC with health-care professionals, with a frustration expressed at the difficulties in obtaining a diagnosis of LRRC, and this impacting upon the doctor-patient relationship [194]. Similar experiences are expressed on Internet forums, whereby patients perceive some healthcare professionals delivering a pessimistic outlook following the diagnosis of LRRC with this having a subsequent negative effect on the doctor-patient relationship. Other opinions expressed on the Internet forums include the impact of LRRC on personal relationships including spousal and family relations, with an emphasis on these roles changing towards more of a carer status.

2.4.2.7 Communication

Wright et al reported patient experiences following treatment for LARC or LRRC, with a number of patients reporting difficulties in communication with healthcare professionals, with regards to investigating new symptoms and referral to specialist services [194]. This is echoed across a number of cancer support group forums, on which the majority of the discussion revolves around the lack of communication between specialist services and primary care or referring consultant, leading to inappropriately long periods of waiting, perceived delays in treatment and subsequent anxiety. The general lack of communication leads to misperceptions regarding treatment intent, disease biology and prognosis amongst patients.

2.4.2.8 Sexual Function

Sexual function is defined as the ability to enjoy and engage in sexual activity. The impact on sexual function was reported by four studies using a combination of qualitative and quantitative measures, including the use of EORTC QLQ-CR38 and ad hoc questionnaires [185, 189, 193, 195].

Holman et al investigated the post-operative sexual function in 10 women who had undergone vaginal reconstruction following surgery for LRRC or LARC through the use of qualitative interviews and established quantitative assessment tools [195]. Two women in this group reported sexual function as satisfactory, describing intercourse as ‘pleasant’. In 40% of women sexual intercourse was difficult due to technical reasons, with the neovagina being too small or suffering complications of surgery leading to sexual difficulties [195]. There is significant anxiety experienced prior to embarking upon a sexual relationship following surgery and vaginal reconstruction, this is due to a combination of fear of using the neovagina and potential changes in sexual relationships [195]. This group of authors also explored sexual function in 5 men, reporting poor sexual functioning in men undergoing perineal reconstruction using a vertical rectus abdominis myocutaneous flap for LARC or LRRC compared to no reconstruction for LARC [195]. Mannaerts et al reported an adverse effect on sexual function

following surgery for LRRC, reporting a reduction in sexual activity from 68% pre-operatively to 32% post-operatively (p=0.000) [190]. Similarly, Guren et al reported significant post-operative sexual dysfunction in patients with LARC/LRRC involving the genitourinary system, with 8 out of 9 males in the treatment group reporting erectile dysfunction [193].

2.5 Discussion

This is the first systematic review to focus exclusively on HrQoL outcomes in patients with LRRC. The current literature reports the impact of LRRC on a wide range of HrQoL domains, including physical, psychological and social aspects. The complex management of LRRC including surgery (curative or palliative), the use of re-irradiation, intra-operative radiotherapy and chemotherapy has a detrimental effect on a wide range of HrQoL domains as well as having an impact upon financial circumstances, relationships with others and communication with health care professionals.

There are only three studies in the current literature which focus exclusively on HrQoL and symptom control in patients with LRRC [27, 187, 188]. All the other studies report mixed outcomes on patients with LRRC, LARC and recurrent gynaecological malignancies. Although LARC and LRRC share some similarities in terms of diagnostic pathway and operative management, LRRC is a distinct clinical entity. LRRC has a distinct clinical course, with a tailored management strategy utilising a range of interventions including surgery, radiotherapy, intraoperative radiotherapy and chemotherapy dependent on treatment goals which may include cure, palliation of symptoms or improvement of HrQoL. LRRC is associated with poor clinical outcomes compared to LARC, with fewer radical resections, greater morbidity and poor overall survival [17, 177, 200, 201]. Due to the inherent differences in the disease biology and clinical course and outcomes of these two distinct clinical entities, it can be inferred that HrQoL outcomes may be different between the two groups, thus making it difficult to correctly interpret current literature. Differences between the two have been

illustrated in the current literature, with Mannearts et al demonstrating a higher degree of post-operative morbidity, social handicap and functional impairment in LRRC patients compared to LARC patients [190].

The assessment of HrQoL is not uniform across the different studies reviewed, with baseline assessments being taken at a variable time periods following diagnosis or treatment of LRRC, with a median time interval of 1-149 months to initial assessment. Seven of the reported studies were retrospective in nature, with initial assessments taken at a median time interval of 11-149 months, as a result of this long lapse in time, assessments may have been subject to recall bias, with the potential of positive experiences reported by the survivors of LRRC participating in these studies. In the three published prospective studies and two abstracts, only three studies provided pre-treatment baseline HrQoL scores, with only 5 patients out of 45 with pre-treatment scores reported by Esnaola et al [188] and 54 out of 105 patients with similar scores in the study by You et al [187]. The lack of baseline data makes it difficult to assess the impact of different interventions on overall HrQoL and to assess the patient perceived risk-benefit ratio.

Twelve of the studies included in the review were quantitative, basing HrQoL scores on a range of assessment tools, which included FACT-C, EORTC QLQ-CR29 and CR38, EORTC QLQ-BLM30, SF36 II and BPI. SF36 II is a generic measure of HrQoL, which is most commonly used in a wide variety of diseases [202]. The BPI is a similar generic tool used to assess clinical pain in a variety of disease scenarios, including cancer, and has been proven to be psychometrically proficient in producing valid and reliable findings [203, 204]. However, the disease-specific measures used by the studies including FACT-C, EORTC QLQ-CR38 and QLQ-CR29 are validated for primary colorectal cancer, across a range of cancer stages (Stage I – IV) and languages [143, 145, 205-211]. The EORTC QLQ-BLM30 was developed to measure HrQoL in bladder cancer [212]. It has not previously been used to measure urological outcomes in patients with LRRC or LARC, and therefore the results from

this study must be interpreted cautiously. Generic HrQoL assessment tools are designed to assess HrQoL in a broad range of populations. Disease-specific HrQoL are used to measure outcomes in specific disease populations. As a result, disease specific HrQoL measures have enhanced capability of detecting and evaluating subtle changes and differences between patient and treatment groups [170, 213]. There are currently no disease-specific measures available to measure HrQoL in LRRC. The use of disease-specific HrQoL tools for primary rectal cancer is an inappropriate measure to assess outcomes in patients with LRRC. Data is of little value unless it has been obtained by the use of a validated questionnaire of proven applicability in the context concerned.

There is little qualitative data available on the experiences of patients with LRRC. The only qualitative study identified was by Wright et al, which involved three out of ten patients with LRRC [194]. The study identified six themes, which included; 1. All that is important is your health, 2. Limited options, 3. Believe in your own intuitive sense of body, 4. Unanticipated morbidity, 5. Mistaken perception of cure and 6. Appropriately and timely information needed. These themes are not echoed in the current quantitative HrQoL assessment tools, suggesting LRRC has a different impact upon patients HrQoL compared to primary rectal cancer. On consultation of Internet support group forums, the emphasis tends to be on communication, the need for information and relationships between patients and healthcare professionals. This suggests further qualitative work is required to identify relevant HrQoL and PROs in this group of patients, prior to the development of a disease-specific assessment tool, which will generate meaningful and relevant data. Holman et al used mixed methods to explore outcomes in patients undergoing vaginal and perineal reconstruction following surgery for LRRC and LARC [195]. This group used qualitative interviews exclusively in 10 women, focusing on sexual function and related outcomes. This is the first study to explore this theme in detail and therefore makes a significant contribution to current literature. However, the lack of similar qualitative data in men makes it difficult to draw any conclusions regarding gender differences in sexual function and overall impact on HrQoL following surgery for LRRC.

There are a number of limitations to the current literature, some of which are common throughout all the studies (Table 2.3). No disease specific measures were used, with only one study defining HrQoL [192]. The quality of the studies included in this review are generally poor, with the majority of studies scoring 5 on the Newcastle-Ottawa Scale, with only one study deemed to be of 'good' quality, with a score of 7 [191]. This combined with the majority of the studies being retrospective in nature has inherent bias associated with it. Furthermore, the use of non-validated HrQoL tools used to assess outcomes in mixed populations makes it difficult to draw any firm conclusions regarding the impact of LRRC and its treatments on HrQoL.

Despite, the high compliance to HrQoL measures of over 64% in the identified studies, which is a crucial methodological requirement to avoid bias in results, the small numbers of patients involved in these studies mean they are usually underpowered to detect statistical and clinically significant differences. Twelve studies reported the method of analysis, with only 3 studies outlining the handling of missing data and only half of the studies taking into account the clinical significance of HrQoL scores. These issues are essential to understanding whether there are any systematic differences between groups in HrQoL scores. The use of clinical significance in these studies helps the interpretation of results on a more meaningful basis and from a patient perspective, rather than simply from the position of statistical significance.

2.6 Conclusion

Current literature on HrQoL in LRRC provides an insight into the wide-ranging impact of this disease process and its subsequent management, despite the limitations in study methodology. To overcome these limitations, a disease-specific, validated and reliable outcome measure is required to provide robust data outcomes in this cohort of patients. This tool must then be used in a study incorporating a

large sample size of patients in a dedicated study measuring HrQoL outcomes across a range of centres and management strategies to truly elucidate the impact of LRRC on HrQoL. Measuring HrQoL using robust methodology will inform healthcare policy and current treatment guidelines and will provide information and understanding of patient specific needs. This will allow for a multidimensional emphasis to be placed on the management on LRRC, taking into account patients needs as well as disease specific goals i.e. cure or palliation, which will in turn improve patient outcomes and HrQoL. In the complex management of LRRC, PROs including HrQoL will inform the role of further radicalisation in the continuing evolution of the management of this disease process.

3 Chapter 3 - Systematic Review of Health-Related Quality of Life in Patients undergoing Pelvic Exenteration

3.1 Background

Pelvic exenteration (PE) whereby there is complete or partial removal of all of the pelvic viscera, vasculature, musculature and ligaments and part of the pelvic bony ring, is the second commonest operation carried out to ensure cure in patients with LRRC [15]. This radical operative procedure is not only reserved to achieve cure in LRRC, but is also used in a number of other advanced pelvic malignancies, including primary rectal cancer, gynaecological malignancies including ovarian, vulval, cervical cancer and urological malignancies including bladder and prostate cancer. PE can be divided into total pelvic exenteration (TPE) or partial pelvic exenteration (PPE). TPE involves the removal of all pelvic organs, which necessitates the construction of two stomas. PPE can be further subdivided into anterior or posterior exenteration; the uterus, adnexa and bladder are removed during anterior PE, while the uterus and rectum alone are removed during a posterior PE.

The differing tumour biology between different pelvic malignancies requiring a pelvic exenteration is reflected in the survival outcomes observed, with 5 year survival of 46-66% in primary rectal cancer [177, 200, 214, 215], 8-42% in LRRC [17, 200, 216, 217] and 45-56% in cervical cancer [200, 218]. However, it can be assumed the HrQoL issues posed by undergoing this operative intervention are common to all groups of patients, irrespective of underlying disease pathology due to the impact of the operation itself.

In recent times, there has been an improvement in the overall survival in patients undergoing PE. This is attributed to improvements in radiological staging, better patient selection, greater use of neoadjuvant chemoradiation and advances in surgical technique. This has obvious implications on cancer survivorship with a greater proportion of patients presenting post-operatively to healthcare professionals with a range of physical and psychological issues. It is therefore essential to document and understand HrQoL issues relevant to this cohort of patients.

3.2 Aims

The aims of this review were to undertake a comprehensive and systematic review of the current literature on HrQoL in patients undergoing a PE, to identify the key HrQoL issues in this population and which instruments were used to measure these outcomes.

3.3 Methodology

This systematic review was conducted according to a pre-specified protocol based on guidance from the Centre for Reviews and Dissemination [219] and the Cochrane Handbook [220]. The review is reported in line with the PRISMA statement[221].

3.3.1 Search Strategy

Literature searches were performed in three databases: MEDLINE (1975 - January 2013), EMBASE and CINAHL. The searches were limited to the English language. The major subject heading, PE, was combined with 'health-related quality of life' or 'quality of life' or 'body image' or 'physical distress' or 'psychological distress' or 'physical function' or 'psychosexual' or 'questionnaires'.

The search was designed to identify qualitative research that explored patients' subjective experience and quantitative studies that measured HrQoL using standardised measures.

Study Inclusion Criteria

Studies were included if they fulfilled the following criteria; they reported outcomes of patients undergoing PE, including symptom control, HrQoL outcomes and impact on function. Patients undergoing surgery and palliative treatments were included. Studies were excluded if HrQoL or functional outcomes were not measured. Case reports, reviews and letters were excluded.

Selection of Studies

Abstracts from studies retrieved were screened for relevance; studies that did not meet inclusion criteria at this stage were excluded. Studies assessed as potentially relevant, or where relevance was ambiguous, were obtained in full, for further scrutiny.

3.3.2 Data Extraction

Data extraction was conducted independently by two reviewers (Deena Harji, DH and Ben Griffiths, BG) into a pre-specified data sheet. Any discrepancies in data extraction were resolved through discussion and consultation with an independent reviewer. The following information was extracted from each study; first author, year of publication, study population characteristics, number of patients, study design, HrQoL assessment tool used, median time interval between diagnosis/treatment and assessment, main findings and quality of study.

3.3.3 Data Quality

The methodological issues surrounding the quality of the studies assessing and measuring HrQoL and functional outcomes in PE were considered A pragmatic approach was undertaken to include all studies reporting HrQoL outcomes and patient testimony irrespective of the quality of the study, due to the sparsely available literature on this topic. However, a quality analysis was undertaken of all published quantitative and qualitative studies.

Qualitative analyses were carried out in accordance with the Critical Appraisal Skills Programme Checklist (CAPS) for qualitative data[222, 223]. This is a checklist consisting of 10 questions which assesses the rigour, credibility and relevance of the qualitative data. Quantitative data was assessed against the Newcastle-Ottawa Scale (NOS) for assessment of non-randomised studies [182]. The NOS contains eight items, categorised into three dimensions including selection, comparability and

outcome for cohort studies or exposure for case control studies. A star system is used to allow a semi-quantitative assessment of study quality; the NOS star ratings range from 0-9, with a rating of 7 or more indicating a high quality study.

3.3.4 Data Analysis

All studies were evaluated for the following criteria; a definition of HrQoL, use of a valid and reliable instrument, compliance issues, handling of missing HrQoL data, reporting of statistical methods, examination of clinical significance and detailed reporting of results.

A combined synthesis of qualitative and quantitative research was performed. This involves generation of a priori distribution of factors and their relative importance using the principles of content analysis to generate common categories and themes from the study findings [224, 225]. The principles of triangulation for integrating mixed methods data were used to determining consistency between findings from each data set [183, 184]. A meta-synthesis of the qualitative data was carried out, with all relevant findings grouped together. Common categories and themes were identified from the study findings. A category was determined by grouping similar findings reflecting similar underlying constructs. In turn categories were synthesised into themes, if they were sufficiently similar, this enabled the summary of all evidence for a particular domain. The same process was carried out for the quantitative data, with findings from the quantitative data set encoded to the categories identified from the meta-synthesis if appropriate, or to new categories. This process enabled comparison between findings from the two types of data sets (qualitative and quantitative), thus enabling the review of all emerging categories and assessing for consistency, discrepancy and complementarity between two the data sets.

3.4 Results

The search strategy identified a total of 194 references. Thirty-six duplicates and 138 inappropriate references were identified through examining the abstracts and were excluded (Figure 3.1). The remaining 20 abstracts were retrieved for further evaluation, of which 19 were included in the review. Studies were excluded if they did not have sufficient details regarding PROs in this cohort. This identified a total of 585 patients who had undergone a PE for a variety of advanced pelvic malignancies. Four hundred and seventy three (80.8%) patients underwent surgery for gynaecological cancer, 21 (3.6%) patients for colorectal cancer, 20 (3.4%) patients for LRRC, 15 patients for a primary rectal cancer or LRRC (2.5%), 15 (2.5%) patients for urological cancer and 8 (1.4%) for anal cancer. The origin of the pelvic malignancy is unknown in 33 (5.6%) patients. A total of 27 (4.6%) men and 427 (72.9%) women participated in the studies. The gender of participants is unknown in 131 (22.3%). Overall median age at the time of completing questionnaires or participating interviews was 54 years.

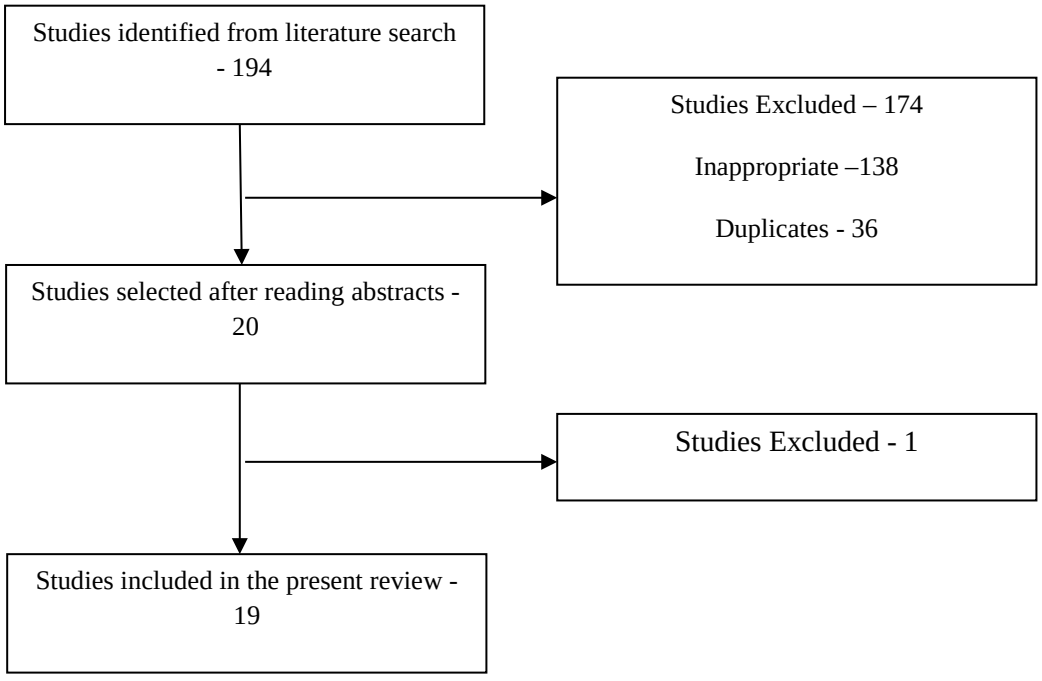


Figure 3-1 Flowchart of Studies Retrieved From Literature Search

Of the 19 studies identified, 5 were qualitative studies [226-230] and 14 were quantitative studies [186, 191, 231-242]. Study design included 12 retrospective cohort studies, 1 retrospective case-control study, 5 prospective longitudinal studies and 1 prospective cohort study. A summary of the main points of each study is highlighted in Table 3.1, with quality analysis of all studies outlined in Table 3.2 and Table 3.3. Overall, the quality of the qualitative studies included in this review were of good quality with 50-90% compliance with the CASP checklist. The quality of the quantitative studies was variable, with the majority of studies scoring over 4 on the NOS scoring system; only one study was identified to be of poor quality with a score of 3 [233] and two studies identified to be of good quality [235, 237].

Table 3-1: Summary Findings of Studies Included Assessing HrQoL in PE

Author and Year	Cancer Type	No of Patients	Median Age	Sex M:F	Study Design	HrQoL Assessment	Median Time Interval Between Diagnosis/ Treatment and Assessment	Assessment Intervals	Main Findings
Dempsey[226] *1975*	Gynaecological malignancy	16	50	0:16	Prospective Longitudinal Study	Qualitative Interview	Pre-operative Assessment	No comment	Post-operatively patients were able to resume their pre-operative occupational, recreational and social status.
Vera [227] *1981*	Gynaecological malignancy	19	51	0:19	Retrospective Cohort Study	Qualitative Interview	6 months - 9 years	One off assessment	Women reported long term impact on sexual function and on occupational and social activities. However, despite that all patients stated their lives had improved following surgery and believed they would continue improving.
Corney [228] *1993*	Gynaecological malignancy	8	55	0:8	Retrospective Cohort Study	Qualitative Interview	30	One off assessment	66% of women complained of sexual dysfunction post-operatively with lack of sexual desire being the commonest issue.
Mirhashemi [229]	Gynaecological malignancy	9	41	0:9	Retrospective Cohort Study	Symptom scales	No comment	One off assessment	78% of women undergoing PE and vaginal reconstruction had resumed sexual intercourse in the post-operative period and were satisfied

2002									with overall sexual function.
Carter [230] *2004*	Gynaecological malignancy	6	57	0:6	Retrospective Cohort Study	Qualitative Interview	4 - 44 months	One off assessment	Patients reported a decrease in sexual activity and interest combined with difficulties in body image. However, an improvement in mood, an increase in activities and adaptation to stomas was noted over time.
Love [231] *2013*	Primary rectal cancer and locally recurrent rectal cancer (15) / Anal (8)/ Gynaecological (2)	26	62	0:26	Retrospective Cohort Study	Sexual Function Vaginal Changes Questionnaire (SVQ)	26 months	One off assessment	14% of patients were sexually active in the post-operative period.
Rezk [232] *2012*	Gynaecological malignancy	16	58	0:16	Prospective Longitudinal Study	EORTC QLQ-C30/ EORTC-QLQ CR38/ EORTC QLQ-BLM30/ BFI/ BPI-SF IADL/ CES-D/ IES-R	Pre-operative Assessment	3 monthly	QoL declined at 3 months but returned to baseline at 12 months, including the ability to perform instrumental daily activities, sexual function and role function.
Guimaraes [233] *2011*	Gynaecological malignancy	13	58	0:13	Retrospective Cohort Study	Symptom Scales	8 months	One off assessment	All patients achieved pain control, with a reduction in the use of opioid analgesia and control of malodorous discharge.
Forner [234] *2011*	Gynaecological malignancy	100	56	0:100	Retrospective Cohort Study	SF12	37 months	One off assessment	Comparable QoL scores between patients undergoing an ileal conduit and ileocaecal pouch for a PE

Zoucas [186] *2010*	Colorectal/ Anal/ Ovarian/ Cervical/ Uterine/Sacral/ Prostatic	22	-	-	Prospective Longitudinal Study	EORTC QLQ-C30	4 months	4 and 16 months	HrQoL improved at 16 months post-operatively.
Austin[191] *2010*	Primary rectal cancer and locally recurrent rectal cancer	37	62	16:21	Retrospective case-control cross-sectional study	FACT-C/SF36 II	47 months	One off assessment	Patients undergoing PE had similar QoL scores compared to patients undergoing anterior resection or abdominoperineal excision.
Hawighorst [236] *2004*	Gynaecological malignancy	129	47	0:129	Prospective Cohort Study	Cancer Rehabilitation Evaluation System (CARES)/Preoperative Anxiety (STAI)	Pre-operative Assessment	One off assessment	Women due to undergo PE had poor preoperative QoL compared to women due to undergo a Wertheim procedure. Patients with high preoperative levels of anxiety had significantly poorer physical and psychosocial functioning, and reported poor medical interaction.
Hawighorst-Knapstein [235] *2004*	Gynaecological malignancy	64	47	0:64	Prospective Longitudinal Cohort Study	Cancer Rehabilitation Evaluation System (CARES)/ Strauss-Appelt Body Image	Pre-operative Assessment	4 and 12 months	Patients undergoing PE requiring two stomas had poorer quality of life and body image compared to those with one stoma or those undergoing Wertheims hysterectomy.

Hawighorst-Knapstein [237] *1997*	Gynaecological malignancy	28	49	0:28	Prospective Longitudinal Study	Cancer Rehabilitation Evaluation System (CARES)/ Strauss-Appelt Body Image	Pre-operative Assessment	4 and 12 months	Patients with two stomas had poor quality of life one year post-operatively, compared to patients with one stoma or no stomas.
Roos[238] *2004*	Gynaecological/ Urological malignancy	25	60	0:25	Retrospective Cohort Study	EORTC QLQ-C30/ EORTC QLQ-OV28/ Symptom scales	59 months	One off assessment	Women undergoing PE had poor physical, social and role functioning with a greater degree of financial difficulty compared to healthy Danish controls and women with cervical cancer. Total exenteration had a greater impact on role and social functioning, on body image and attitude towards the disease compared to partial exenteration.
Woodhouse [239] *1995*		10			Retrospective Cohort Study	Symptom Scales	No comment	One off assessment	80% of patients achieved excellent palliation of symptoms following PE.
Brophy [240] *1994*	Colorectal(21)/ Urinary (9)/ Gynaecological malignancy (5)	35	60	11:24	Retrospective Cohort Study	Symptom Scales	Pre-operative Assessment	One off post-operative assessment	88% of patients reported an improvement in QoL. 60% achieved control of pain and 50% of patients achieved control of symptoms of bleeding and fistulae.
Gleeson [241] *1994*	Gynaecological malignancy	8		0:8	Retrospective Cohort Study	Symptom Scales	15.5 months	One off assessment	87.5% of women reported long term sexual dysfunction, with 37.5% complaining of long term symptoms

									of vulval pain.
Andersen[242] *1983*	Gynaecological malignancy	15	54	0:15	Retrospective Cohort Study	Symptom Checklist-90/ Beck Depression Inventory /Katz Social Adjustment Scales/ Marital Adjustment/ Derogatis Sexual Functioning Inventory/ Heterosexual Behaviour Hierarchy/ Sexual Arousal Inventory	5 years and 6 months	One off assessment	Women report long term sexual dysfunction, with symptoms of mild depression however were well adjusted socially, reporting active social lives.

Table 3-2 Quality Assessment of Qualitative Studies

Author	Clear Statement of Aims	Is Qualitative Methodology Appropriate	Was the research design appropriate to address the aims of the research?	Was the recruitment strategy appropriate to the aims of the research?	Was the data collected in a way that addressed the research issue?	Has the relationship between researcher and participant been adequately considered?	Have ethical considerations been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	How valuable is the research?
Dempsey [226]	•	•	•	•	•				•	•
Vera [227]	•	•	•	•	•				•	•
Corney [228]	•	•	•	•	•				•	•
Mirhashemi [229]	•	•	•	•					•	
Carter [230]	•	•	•	•	•	•		•	•	•

Table 3-3 Quality Assessment of All Quantitative Studies

CASE-CONTROL STUDIES				
	SELECTION	**COMPARABILITY**	**EXPOSURE**	**OVERALL SCORE**
Forner [234]	**	*	***	6
Austin [191]	***	**	**	7
Roos [238]	**	*	**	5
COHORT STUDIES/CASE SERIES				
	SELECTION	**COMPARABILITY**	**OUTCOME**	**OVERALL SCORE**
Love [231]	***		*	4
Rezk [232]	***	*	**	6
Guimaraes [233]	*		**	3
Zoucas [186]	**	*	**	5
Hawighorst [236]	***	*	**	6
Hawighorst-Knapstein [235]	****	*	**	7
Mirhashemi [229]	**		**	4
Hawighorst-Knapstein [237]	****	*	**	7
Woodhouse [239]	**		**	4
Brophy [240]	**		**	4
Gleeson	**		**	4
Andersen	**		**	4

HrQoL was the main primary endpoint in 12 studies [191, 226-228, 230-232, 235-238, 242], however only one study defined the meaning of HrQoL [235] (Table 3.4). Compliance with completion of HrQoL assessments was reported in 73% of studies included in this review, with reported compliance ranging from 46-100%. Baseline assessments of HrQoL assessments prior to the initiation of treatment were available in six studies [231, 232, 235-237] [226], with the majority of assessments being carried out at a median timeframe of 4-59 months. Two studies had a long lag period between treatment and assessment of HrQoL undertaking assessments at 5.5 and 9 years respectively [227, 242].

Table 3-4 Statistical and Design Issues in Studies Assessing HrQoL

Author	Definition of HrQoL	Primary Outcome	Compliance	Handling of Missing Data	Baseline Characteristics Reported	Method of Analysis Reported	Follow-Up Data Reported	HrQoL significance addressed	HrQoL significant
Dempsey [226]	No	HrQoL	69%	Not reported	Yes	No	N/A	No	No
Vera [227]	No	HrQoL	76%	Not reported	No	No	N/A	No	No
Corney [228]	No	HrQoL	76%	Not reported	No	No	N/A	No	No
Mirhashemi [229]	No	Clinical	Not reported	Not reported	No	No	N/A	No	No
Carter [230]	No	HrQoL	55%	Not reported	No	Yes	N/A	No	No
Love [231]	No	HrQoL	87%	Not reported	Yes	Yes	Yes	Yes	Yes
Rezk [232]	No	HrQoL	80%	Not reported	Yes	Yes	Yes	Yes	Yes
Guimaraes [233]	No	Clinical	100%	N/A	No	No	No	No	No
Forner [234]	No	Clinical	Not reported	Not reported	No	No	No	No	No

Zoucas [186]	No	Clinical	Not reported	Not reported	No	Yes	Yes	Yes	Yes
Austin [191]	No	HrQoL	84%	Not reported	No	Yes	N/A	Yes	No
Hawighorst-Knapstein [235]	No	HrQoL	52%	Not reported	Yes	Yes	Yes	Yes	Yes
Hawighorst-Knapstein [237]	Yes	HrQoL	46%	Not reported	Yes	Yes	Yes	Yes	Yes
Hawighorst [236]	No	HrQoL	Not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Roos [238]	No	HrQoL	86%	Not reported	No	Yes	No	Yes	Yes
Woodhouse [239]	No	Clinical	100%	N/A	No	No	Yes	No	No
Brophy [240]	No	Symptom Control	Not reported	Not reported	Yes	No	Yes	Yes	Yes
Gleeson [241]	No	Functional	50%	Not reported	No	No	Yes	No	No
Andersen [242]	No	HrQoL	100%	Not reported	N/A	Yes	N/A	No	No

Quality of Life Trajectory

Four prospective longitudinal studies were identified which highlighted the HrQoL trajectories experienced by patients undergoing PE [186, 232, 235, 237], of these 4 studies, 3 studies had pre-operative baseline data [232, 235, 237]. All four studies reported similar patterns of recovery of HrQoL domains, with an initial deterioration in HrQoL scores in the immediate post-operative period of 3-4 months, followed by a gradual improvement or a return to baseline scores at 12-16 months post-operatively. Rezk et al reported poor scores of emotional function, insomnia, future perspectives and stress-related ideation at baseline, with continuing improvement in these scores at 3 months and 12 months, with the worse scores observed at baseline [232].

Total versus Partial Pelvic Exenteration

Patients undergoing a TPE experience a greater degree of post-operative morbidity due to the greater radicality the operative approach necessitates which in turn has an adverse effect on HrQoL outcomes, compared to patients undergoing a PPE. Supporting evidence for this comes from Hawighorst-Knapstein et al, who reported poor overall HrQoL outcomes in patients with two stomas compared to patients with one stoma, with deteriorating HrQoL scores in the this group during the first 12 months post-operatively, compared to improvement in these scores in the latter group [235, 237]. Similarly, Roos et al reported lower HrQoL scores observed in patients who underwent a TPE compared to a PPE, with the greatest differences observed in the domains of role functioning, social functioning, body image and attitude towards disease [238].

3.4.1 Identified HrQoL Themes

One hundred and eighty four findings, 33 categories and 9 themes were identified through scrutiny of the literature (Table 3.5).

Table 3-5 Synthesised Categories and Themes Identified

Theme	Category
Body Image	Adjustment to bodily changes Attractiveness Self-image Self-confidence
Social Impact	Disruption of activities of daily living Reduction in social and recreational activities
Sexual Function	Interest in sex and sexual activities Sexual satisfaction Physical difficulties with sexual intercourse Psychological difficulties with sexual intercourse Sexual difficulties affecting relationships
Treatment Expectations	Length of recovery Pain expectations Complications Treatment intent Cure and disease recurrence
Symptoms	General Health Gastrointestinal Symptoms Stoma issues and complications Pain
Communication	Communication with partner Communication with medical professionals Need for medical information
Psychological Impact	Impact on mental and emotional well being Future Perspective

	Anxiety
Relationships	Change of role Dependence on others Adjustment of relationships Relationship with medical professionals
Work and Finance	Occupational recovery Financial difficulties Adaptation of work environment to accommodate restrictions imposed upon by surgery

3.4.1.1 Body Image

Four studies, consisting of 133 (22.7%) female patients undergoing PE for gynaecological (95.5%) or urological (4.5%) malignancy, reported the impact of PE on body image [232, 235, 237, 238]. Two of these studies used the Stauss and Appelt Body Image questionnaire to evaluate the impact on body image [235, 237]. The remaining two studies reported the impact on body image using items from the European Organisation for Research and Treatment of Cancer colorectal cancer specific module QLQ-CR38 and the EORTC QLQ-OV28 ovarian cancer specific module [238].

Two prospective, longitudinal studies, reported an initial deterioration in body image scores, with improvement towards baseline scores at 12 months [232, 237]. A third prospective, longitudinal study of 64 women with gynaecological malignancy reported deteriorating scores of attractiveness and self-confidence in the first post-operative year, with baseline scores of 11.4 compared to 12 month scores of 9.96 on the Stauss and Appelt Body Image questionnaire, $p=0.000$ [235]. Patients with two stomas had higher scores concerning body uncertainty/discomfort and less attractiveness/self-confidence 12 months post-operatively compared to the pre-operative period [235, 237]. Furthermore, these scores were statistically significantly higher in this cohort of patients compared to patients with one or no stomas ($p<0.05$) [235, 237, 238]. Age did not have an impact

upon perceptions of body image [238]. Patients undergoing surgery for primary gynaecological or urological malignancy had lower scores for negative body image compared to patients undergoing surgery for recurrent malignancy [238].

3.4.1.2 Social Impact

Seven studies, four quantitative [24, 232, 238] and two qualitative [226, 227], commented upon the impact of PE on social function. Rezk et al documented an initial decline in social functioning scores, with gradual improvement over time and a return to baseline scores at 12 months post-operatively [232]. Austin et al reported no differences in post-operative social well being between patients undergoing PE and surgery for primary rectal cancer [191].

The earliest qualitative studies on patients undergoing PE was carried out in the 1970s by Dempsey et al [226]. This group conducted qualitative interviews with 17 women who had undergone PE for gynaecological malignancy. All women in this study reported resumption of previous hobbies and social activities in the post-operative period, however it took a prolonged period of time to resume slightly more vigorous activities such as bowling, and an adaptation to other activities such as swimming [226]. Furthermore, this group of patients reported no change in social interactions and relationships [226]. Andersen et al reported similar findings, with the majority of patients resuming social activities, however did comment upon a subset of patients adapting their social activities to accommodate their post-operative functional status [242]. Furthermore, women who were able to maintain social activities post-operatively displayed lower levels of psychological distress [242].

3.4.1.3 Sexual Function

Twelve studies reported the impact of PE on sexual function using a variety of questionnaires and semi-structured interviews, with conflicting results. These 12 studies reported the findings of 240

women who underwent PE for gynaecological (87.5%), primary rectal or LRRC (6.7%), bladder (2.5%) or anal canal (3.3%) malignancy. Studies reported between 50-100% of women were sexually active pre-operatively, this deteriorated to 12.5-18% in the post-operative period [226-228, 231], with only one study reporting higher rates of post-operative sexual activity [229].

Two of the ten studies reported satisfactory post-operative sexual function following PE [229, 232], with Rezk et al reported the return of sexual function scores to baseline at 12 months following an initial dip in scores at 3 months in 16 women undergoing PE for gynaecological malignancy [232]. Mirhashemi et al reported satisfactory post-operative sexual function in 9 women who had undergone PE with vaginal reconstruction, with 78% of women reporting successful sexual intercourse [229].

Six studies reported significant post-operative disruption in sexual function using a range of quantitative measures [231, 235, 237, 238, 241, 242]. These studies documented deteriorating post-operative sexual function scores in the first post-operative year [235, 237], with poor scores observed in women with two stomas [237, 238]. Furthermore, women undergoing PE had poor sexual function scores when compared to women undergoing Wertheim's hysterectomy [235] and reported a reduction in sexual activity far below the norms provided for sexually dysfunctional women [242]. Four studies explored reasons behind sexual dysfunction following PE using qualitative interviews [226-228, 230], reasons cited for lack of sexual activity, included lack of sexual desire [226-228, 231], vaginal pain, bleeding and dryness [228], difficulties in engaging in intercourse with a neovagina [227, 230] and stomas affecting sexual intercourse [227] . Corney et al reported 46% of women felt moderate-severe mental and emotional distress as a result of their sexual problems [228].

3.4.1.4 Treatment Expectations

Patient treatment expectations are dependent on operative intent i.e. curative or palliative. Patients often view exenterative surgery as the only alternative to death from advanced pelvic malignancy,

viewing this as the only option of potential cure and are therefore willing to accept the risks involved [230].

In appropriately selected patients, PE can be undertaken to achieve appropriate palliation of distressing symptoms [233, 239, 240]. Brophy et al reported an improvement in quality of life in 88% of patients following palliative PE, with 60% reporting improvements in pain control and 50% reporting improvement in bleeding or fistulae [240].

Carter et al reported the qualitative experiences of patients treatment experiences regarding PE surgery, they reported all 6 women were surprised and distressed by the length of recovery and despite adequate pre-operative information felt unprepared regarding complications [230]. Vera et al reported 36.8% of patients reported the general recovery following PE to be the most difficult thing to contend with [227]. Rezk et al reported patients had high expectations of pain pre-operatively, however found pain scores remained static throughout a 12 month post-operative period [232]. The majority of patients in this study also reported their actual recovery time to match up to their expectations, with only 25% of patients reporting a longer than expected recovery time [232].

3.4.1.5 Symptoms

Given the advanced nature of the range of malignancies requiring a PE and the radical nature of the surgery, patients present with and experience a range of symptoms, affecting general health as well as a variety of systems.

- *General Health*

  Overall, general health deteriorates in the initial post-operative period, with patients experiencing greater fatigue and lethargy, however with recovery and time, this returns to normal [232]. Roos et al demonstrated patients undergoing PE reported high scores of fatigue, insomnia and poor appetite, compared to the healthy population and women undergoing surgery for cervical cancer [238]. It is this general deterioration in health which has far reaching effects, with women

reporting this deterioration to be a key factor in the delayed return to normal daily activities including work [226].

- *Gastrointestinal Symptoms*

  Gastrointestinal symptoms, such as abdominal pain and distension are commonly reported in the post-operative period [232, 238]. Rezk et al reported a higher incidence of gastrointestinal symptoms, including flatulence, at 12 months post-operatively [232].

- *Pain*

  Pain is a common complaint amongst patients undergoing PE, with patients typically describing abdominal or pelvic pain. Patients have high expectations of pain in the pre-operative period [232], however pain scores are static in the post-operative period and are comparable to scores in the healthy population [232, 238].

  The distressing symptoms of pain and its wide ranging impact on overall HrQoL, is one of the most common indications for palliative PE [233, 239, 240]. Guimaraes et al reported resolution on pain with a reduction in opioid analgesia use in 13 patients undergoing palliative PE, with reports of an overall 2 year survival of 15.4% [233].

- *Stoma Issues and Complications*

  Overall, the permanence of the stoma in patients undergoing PE is a source of physical and psychological distress, contributing to issues concerning body image and sexual function, engagement in social activities, combined with the practicalities of managing a stoma [226, 227, 230]. Vera et al reported a third of patients undergoing PE found the adaptation of life to accommodate a stoma was the most disruptive aspect of undergoing surgery [227]. However, following a period of adjustment the majority of patients accepted the stoma with resolution of any previous issues [226, 227, 230].

There is conflicting evidence regarding the impact of one permanent stoma as per PPE and two permanent stomas as per TPE. Hawighorst-Knapstein et al reported women undergoing TPE had poor scores of physical, psychosocial, sexual and marital function compared to women undergoing PPE with one stoma (p=0.003) and no stomas (p=0.008) 12 months post-operatively [237]. Similar findings were reported by Roos et al, with poor scores of emotional functioning, social functioning, body image and attitude towards disease documented in patients undergoing TPE compared to PPE ($p < 0.05$) [238]. Conversely, Austin et al reported comparable HrQoL scores between patients undergoing TPE and PPE [191].

To avoid the creation of a second permanent stoma, occasionally a continent pouch can be created as an alternative. Forner et al reported their findings of 59 patients undergoing TPE, of which 22 patients had an ileocaecal pouch constructed as opposed to a traditional ileal conduit, HrQoL scores were higher in the pouch group compared to the stoma group (81 versus 56, p=0.10) [234]. However, operating times were longer in the pouch group, with a greater number of post-operative complications observed.

3.4.1.6 Communication

Corney et al reported 105 women undergoing PE would have liked more information on their disease, operation and recovery [228]. Furthermore, 28% of women would've like more information regarding sexual matters and a further 26% of women felt their partner had received inadequate information [228]. Similarly, Carter et al, reported despite women receiving information pre-operatively, they felt it was inadequate in preparing them for their post-operative recovery and potential complications [230].

Dempsey et al and Vera et al reported upon the communication with and impact upon partners; reporting a range of reactions, from shock and grief to hope [226, 227]. All patients in a relationship

found the communication between themselves and their partner to be a great source of support [226, 227]. Conversely, Carter et al reported women found it difficult and uncomfortable discussing surgery and the subsequent body changes with their families and wider social circle due to feelings of embarrassment, shame, stigma and fear of rejection [230].

Hawighorst et al explored the patient-physician relationship pre-operatively in women undergoing surgery for gynaecological malignancy [236]. They found no differences in medical interaction between women due to undergo a PE compared to a Wertheim hysterectomy [236]. However, they did report women expressing higher levels of anxiety stated a significant lack of medical explanation, expressed more difficulties in understanding medical information, asked doctors more questions and felt helpless in the medical setting [236].

3.4.1.7 Psychological Impact

The psychological impact of PE and the emotions expressed by patients is a dynamic process, with different emotions expressed at different stages of treatment. Qualitative research in this field reports initial emotions of shock and fear, followed by an acceptance and a hope for cure, with occasional symptoms of sadness and depression in the preoperative period [226, 227]. Motivating factors cited during this period are based on watching families growing up and the resolution of symptoms. Immediate postoperative feelings and emotions are generally negative, with feelings of depression regarding the future and bodily changes, feelings of frustration and loss of independence and worries regarding the impact upon others [226, 227, 230]. Vera et al explored the long term psychological impact following PE surgery, and found patients generally felt their lives had improved following surgery and would continue to improve, with a great deal of hope expressed [227].

A number of authors have used quantitative measures to assess psychological impact, with similar results to qualitative data. Rezk et al reported stress-related ideation and patients perspective for the future were at there worst during the pre-operative period and improved significantly during the first

12 months post-operatively [232]. Furthermore, the same authors observed a decline in post-operative depression levels over the same time frame [232]. Similar findings were reported by Hawighorst-Knapstein et al, who reported a reduction in psychosocial scores over 12 months in patients undergoing PPE, however in patients undergoing TPE, these scores deteriorated much more significantly [235, 237]. The same group of authors examined the effects of pre-operative anxiety of HrQoL, and found women expressing higher levels of anxiety had poor scores in HrQoL domains compared to women with moderate levels of anxiety, irrespective of the operative procedure [236].

3.4.1.8 Relationships

Personal and marital relationships are most affected by exenterative surgery, with a range of outcomes. Early reports from Vera et al suggested a small proportion of patients were abandoned by their spouses following diagnosis and impending surgery, however the majority of partners expressed initial support and were hopeful of cure [227]. Dempsey et al reported similar reactions by both the patients' and their husbands' to the initial diagnosis, with all husbands going on to play a supportive role subsequently [226]. Corney et al explored the impact of PE on marital status and sexual function, reporting all 8 women undergoing PE felt their marital satisfaction had improved or stayed the same, however 47% of women indicated a deterioration in their sexual relationship [228]. Andersen et al reported post-operative marital adjustment scores similar to average non-distressed couples at a median of 5 years post-operatively [242].

PE surgery can have an adverse effect on personal relationships, due to potential changes in roles, bodily changes and sexual function. Roos et al reported higher scores of disruption within relationships in younger women undergoing PE surgery [238], with similar reports from Corney et al who reported the end of 5 marriages in women aged 32-45 following surgery [228]. The presence of two stomas can have a greater impact on marital status, with greater marital disruption in this group compared to patients with one stoma [237]. These adverse effects extend beyond personal relationships and can effect family life and the wider social network, due to changes in role and need

for dependence on others [230]. Carter et al reported the qualitative experiences of 11 women undergoing PE surgery, of which the majority of women were unwilling to share their body image for fear of shame, embarrassment and rejection [230]. The majority of patients in this study felt feelings of guilt and were worried about being a burden upon their families. Similar qualitative research has revealed immediate post-operative concerns involve families and children and the impact of surgery upon them [227].

Patients with high levels of preoperative anxiety have poor relationships with healthcare professionals, with an increased need for medical information [235]. Hawighorst-Knapstein et al documented poor scores of medical interaction pre-operatively, however these improved and remained static at 3 and 12 months post-operatively [235, 237]. The majority patients had a good relationship with their doctor however one qualitative study reported feelings of hatred and anger expressed towards the doctor who made the initial diagnosis [226].

3.4.1.9 Work and Finances

The impact of PE on general health, combined with a potentially lengthy recovery has obvious implications on return to work, occupational recovery and overall financial status. Vera et al reported only 1 patient out of 11 having undergone PE was able to return to her pre-operative employment, with this leading to a decline in overall income in 53% of patients [227]. The most common reason for unemployment was physical illness or disability, followed by limitations imposed by the surgery [227]. Dempsey et al reported 80% of full time workers had been able to return to work, with a 100% of part time workers returning to lighter duties [226]. The documented return to work was staged, with a return to part time duties 2 months post-operatively, followed by return to full time employment in the following months [226].

Concerns regarding financial impact of PE surgery were most prominent pre-operatively, with patients citing this as a source of stress and worry [226, 227]. This is illustrated by Rezk et al, who

documented higher scores of financial difficulties pre-operatively, followed by improvement and stabilisation of these scores in the post-operative period [232].

3.4.2 HrQoL Assessment Tools

Four studies utilised qualitative interviews to determine the impact of PE on HrQoL [226-228, 230]. Of the 15 quantitative studies, a number of different assessment tools were utilised to assess the impact of PE on HrQoL (Table 3.1). Of the 10 quantitative studies utilising existing HrQoL assessment tools 16 generic tools were used. Five studies utilised ad hoc symptom scales, designed specifically for the individual study [229, 233, 239-241]. The EORTC QLQ-C30 questionnaire was used in 3 studies [186, 232, 238] and was combined with the colorectal cancer module, EORTC-CR38 [232], the muscle invasive bladder cancer module, EORTC QLQ-BLM30 [232] and the ovarian cancer module, EORTC OV28 [238]. The Cancer Rehabilitation Evaluation System was used in 3 studies [235-237]. Body image was assessed using the Strauss and Appelt Body Image questionnaire [235, 237]. A range of other assessment tools were used including, the Sexual Function Vaginal Changes Questionnaire [231], Pre-operative Anxiety (STAI) questionnaire [236], Symptom Checklist-90 [242], Beck Depression Inventory [242], Katz-Social Adjustment Scale [242], Dyadic Adjustment Scale [242], Derogatis Sexual Functioning Inventory [242], Heterosexual Behaviour Hierarchy [242], Sexual Arousal Inventory [242], SF36-II [191], FACT-C[191], Short-Form 12 (SF-12) [234], Instrumental Activities of Daily Living (IADL) [232], Centre for Epidemiologic Studies Depression Scale (CES-D) [232], Brief Fatigue Inventory (BF1) [232], Brief Pain Inventory – Short Form (BPI-SF) [232] and the Impact of Events Scale-Revised (IES-R) [232].

3.5 Discussion

This systematic review reveals that PE surgery has a wide ranging impact upon a number of HrQoL domains including physical, psychological and social domains as well as upon body image, sexual

function, communication, relationships, work and finance. The reporting of these domains is variable and is often reported using a variety of different PROMs. Furthermore the study design is often of poor quality, which makes it difficult to interpret the impact of PE surgery on each of these domains.

PE is the only available option in a range of advanced pelvic malignancies, including gynaecological malignancy, urological malignancy and primary and recurrent rectal cancer. This review identified 585 patients of which 80.8% of patients underwent PE for a gynaecological malignancy. This has obvious implications of the findings of this review, given the majority of the findings were reported by women. It is well documented within the literature that women utilise health services and report symptoms more frequently than men [243-245]. The disproportionately high number of women included in the review may impact the themes identified. There were no reports of the impact of body image in men undergoing PE in this review, as the study population of the two studies looking exclusively at body image were made up entirely of women [235, 237]. This has potentially important implications, as healthy women are documented to have poor body image compared to men [246, 247], with these differences potentially exacerbated by surgery. Sexual function was also not reported in the male population, as the majority of studies exploring this theme included female patients alone [228, 229, 231, 241, 242]. Furthermore, the majority of the qualitative work undertaken in patients undergoing PE was carried out in women [226, 227, 230], as a result, little is known about the HrQoL issues, specifically, body image and sexual function, which effect men, and therefore the results of current literature should be interpreted cautiously.

The majority of the qualitative work carried on the impact of PE was undertaken in the 1970s [226] and 1980s [227], with little modern data available. There has only been one study carried out in the 2000s, which identified a different set of HrQoL issues [230] compared to the earlier works of Vera et al [227] and Dempsey et al [226]. In 2004 Carter et al reported 7 themes of recovery, complications, social support, stoma issues, sexuality, disclosure and fear of recurrence [230]. Earlier reports commented on themes of husbands reactions to need for surgery, pre-operative reactions, mood and method of coping prior to surgery, short-term post-operative reactions, occupational recovery, sexual activity and marriage, psychiatric disorders, adjustment to stomas, hobbies and recreation and post-

operative appraisal of life [226, 227]. This suggests modern day qualitative work is required to potentially confirm themes identified by previous works and to establish up to date current HrQoL issues which may effect patients.

Stratifying patients according to the number of stomas created provides important HrQoL data, with poor HrQoL scores observed in patients with two stomas compared to one [235, 237, 238]. However, HrQoL is also dependent on the type stoma, as demonstrated by Forner et al, who reported higher HrQoL scores in patients undergoing continent urinary diversion compared to an incontinent urinary diversion, although these differences were not statistically significant, they may be clinically relevant [234]. More accurate and targeted HrQoL data can be obtained if these patients are stratified according to the type of stoma created. This would lead to five clinically distinct groups; a continent urinary diversion with and without a colostomy, an incontinent urinary diversion with and without a colostomy and a colostomy alone. Being able to provide good quality, prospectively collected HrQoL data on this group of patients will enable and empower patients and inform clinicians during pre-operative decision-making.

The current reporting of HrQoL in patients undergoing PE is variable, with a number of limitations in the study methodology; with the majority of studies being retrospective in nature, little baseline data and long lapses in time between treatment and assessment of HrQoL leading to potential for recall bias. This is reflected in the variable quality of the studies as assessed by the CASP checklist for qualitative studies and NOS for quantitative studies, with only a handful of studies being deemed of good or high quality. The use of a multitude of generic and disease-specific measures makes it very difficult to compare HrQoL outcomes between studies. Furthermore, the majority of disease-specific measures have been used inappropriately in this cohort of patients, as these measures were not originally validated for use in this group of patients. Austin et al were the only group of authors to use an appropriate disease-specific measure, utilising the FACT-C assessment tool in patients undergoing

PE for primary and recurrent rectal cancer [191]. However, FACT-C is only validated for primary rectal cancer [205] and therefore the data obtained for patients with LRRC must be interpreted cautiously as it has not been obtained through validated, reliable means. The use of disease specific measures ensures a sensitive method of detecting changes and differences between patients and treatment groups [170, 213]. Two studies used between 6 [242] and 8 [232] different HrQoL assessment tools. In one study patients were expected to complete this volume of questionnaires at 3 monthly intervals [232], this is associated with significant responder burden, which may potentially have an adverse impact on the results obtained due to potential compliance issues. The use of multiple HrQoL assessment tools is currently used to encompass all the potential issues faced by this cohort of patients, as there is currently no specific assessment tool for patients undergoing PE.

Overall compliance with HrQoL assessments is good with reported rates of 46-100%. However despite this there is a lack of detail regarding statistical analysis of data, with only 10 studies reporting this information [186, 191, 231, 232, 235-238, 240, 242]. Furthermore, no studies reporting the handling of missing of data and only 8 studies addressed the clinical significance of HrQoL prior to study commencement [186, 232, 235, 236] [231, 237, 238, 240]. This is an essential requirement for interpreting data in a meaningful and clinically relevant manner and not just from a statistical perspective.

Overall, the different methodology employed in these studies, combined with the variety of assessment tools used and the variable reporting make it very difficult to compare the results obtained from these studies, and consequently, interpret them in a clinically meaningful manner. The variable reporting of PROs has been highlighted as a consistent issue in clinical research [248, 249], with much work being carried out on standardising reporting outcomes within the context of clinical trials[142]. However, similar work is required to establish a minimum data set which must be adhered to in the reporting of PROs in observational research. This will help standardise PRO reporting and thus potentially enable meaningful comparisons.

3.6 Conclusions

This review consolidates the current literature on the impact of PE, identifying a number of relevant HrQoL issues. However, it highlights a number of shortcomings in the current literature, with the majority of the literature being retrospective in nature, with a long lag time between treatment and assessment. This is combined with the use of inappropriate disease-specific measures to assess different populations of interest. Currently, there is no one specific assessment tool that encompasses all the HrQoL issues which effect patients following PE. More work is required in this field to update the current literature, including qualitative work in men undergoing PE surgery to supplement current data and potentially aid in the development of a disease specific measures for patients with advanced malignancy requiring a PE. Future studies need to be methodologically robust in design and reporting as this is the only way meaningful data can be generated to be used and applied in the clinical setting for this complex cohort of patients.

4 Chapter 4 - Development of a LRRC Specific Conceptual Framework

4.1 Background

PROMs extend patient outcome assessment beyond traditional clinical outcomes, such as survival, adverse effects and treatment efficacy. PRO measures are designed to capture concepts related to the health experience of the individual, in relation to their disease and treatments. HrQoL is a specific type of PRO, and is the commonest type of PRO measure used in clinical practice. This is an area of growing interest in the field of surgical oncology, with an emphasis on the integration of the combined reporting of PRO outcomes and clinical outcomes [88]. PROs in surgery, and specifically, in LRRC, can provide valuable data to inform clinical decision making, improve patient care, improve provision of information and influence health care policy and decision making [250-252].

The documentation of PROs in LRRC is poor; a systematic review of HrQoL in LRRC identified a small number of studies documenting the impact of LRRC on HrQoL, with little integration of clinical and PRO outcomes (Chapter 2).

For a PRO measure to be valid it must be developed in a systematic and scientifically rigorous manner [89, 253, 254]. To be able to capture meaningful and appropriate data, PRO measures must possess content validity. Content validity assesses whether items are comprehensive, understandable and acceptable, and reflect the perspective of the population of interest.

Qualitative data is essential for establishing content validity of a PRO measure. Content validity must be based on direct input from an adequate sample of patients from the target clinical population. To this end, the use of conceptual frameworks have been recommended by a number of regulatory agencies including the Food and Drug Agency [89], The Medical Outcomes Trust [255], International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [256] and the European Organisation for Research and Treatment of Cancer [257, 258]. The development of a new PRO measure is a multi-step process, with the first step being that of identification of concepts and themes relevant to patients with LRRC and the development of a conceptual framework. The conceptual

framework outlines the structure of the concept that a PRO aims to measure and is often depicted diagrammatically, representing the relationships between the overarching concept (HrQoL in LRRC), the identified domains (HrQoL themes) and the items. Establishing content validity is essential in providing evidence that the conceptual framework, content of items and overall measure is consistent with the perspective, experiences and words of the population of interest. Developing a conceptual framework is a two stage process, with the first stage consisting of a systematic review of current literature to identify key themes relevant to the population of interest followed by supplementary qualitative studies. This can be done through the use of focus groups or individual interviews [259]. This approach has been used in developing a conceptual framework for LRRC, two previously conducted literature searches identified 10 key themes relevant to this cohort of patients (Chapters 2 and 3). These searches were supplemented by patient perspective. The development of a robust and accurate conceptual framework is key to the PRO measure, as inadequacies in the framework may lead to inappropriate and incorrect outcome measurements [260].

4.2 Aims and Objectives

The objectives of this study were to:

- Identify HrQoL themes relevant to patients who have undergone surgery for LRRC
- Identify the impact of clinical factors (subsite location, concurrent metastatic disease, adjuvant treatments) on HrQoL
- To develop a conceptual framework for LRRC-specific HrQoL

4.3 Methods

4.3.1 Qualitative Study – Focus Groups

To identify HrQoL themes relevant to patients with LRRC, gender-specific teleconference focus groups were held. All focus groups were held by the same facilitator and were informed by a topic

guide (Appendix 2) based on the previous systematic reviews (Chapter 2 and 3). All focus groups were recorded and transcribed verbatim. Notes were taken throughout each focus group. All patients were offered a debriefing service at the end of the focus group.

A purposive sampling method was devised to aid recruitment, with sampling of patients targeted to key factors to reflect the range and diversity of the target population, including sex, LRRC subsite (anterior, central, lateral or posterior), presence of concurrent metastatic disease and use of multimodal treatments (chemotherapy +/- radiotherapy). A minimum of four patients per key factor were consecutively sought (Table 4.1).

Table 4-1 Purposive Sampling Strategy

Factors	***Number of Patients***
Gender	
Male	12
Female	9
Subsite Location	
Central	7
Anterior	5
Posterior	5
Lateral	4
Concurrent Metastatic Disease	
Yes	5
No	16
Pre-operative Treatments	
None	6
Chemotherapy	4
Chemoradiation	11

4.3.2 Data Analysis

The transcripts were imported into NVivo 10 and coded line by line. NVivo 10 is designed to facilitate the storage, coding and retrieval of qualitative data using Boolean operators.

The principles of thematic content analysis were employed to aid data analysis. This process involves interpreting data and creating codes, categories and themes [225, 261]. This method of analysis was chosen as it enables structured data collection combined with an explicit analytical procedure informed by a priori reasoning based on existing theory and literature [225, 262]. This methodology is in keeping with the objectives of this study, which extended a preliminary conceptual framework based on current literature with new patient reported data.

Concepts that pertain to the same phenomenon are grouped to form categories. Categories are further developed into themes. Using thematic content analysis HrQoL issues were identified from the transcripts and coded in accordance to a provisional coding framework. Identifying a series of codes and then grouping them into similar categories and themes was the systematic approach employed in this study. Analysis was an iterative process during the data collection process, with data from each focus group being analysed immediately. This enabled future focus groups to be informed by the preceding focus group, thus ensuring confirmation of identified codes. Following the first focus group, all subsequent coding was undertaken with the preceding focus group and emerging theory in mind. This continuous analysis ensured that the emerging coding schema was complete and saturated. Saturation is the point in data analysis process where no further information is elicited. To ensure sufficient data was collected to reach conceptual saturation, a saturation grid was devised to track emerging concepts. All coding was reviewed iteratively by a second coder, who was a dedicated qualitative researcher. Any discrepancies in coding were resolved through discussion.

Comparative Analysis

On completion of coding, a comparative analysis was conducted across all identified themes and the patient sample to explore any emerging differences. Any patterns and associations were identified unique to each patient factor i.e. disease subsite, margin status, presence of metastatic disease, use of multi-modal treatments pre and post-operatively and to each study location (Leeds or Sydney).

Expert Review

Following all data analysis, a multidisciplinary expert panel consisting of six surgeons (3 British, 3 Australian), two oncologists, two colorectal nurse specialists, a clinical psychologist and a public health epidemiologist reviewed the proposed conceptual framework. Distinctions were made by the panel regarding HrQoL issues and issues relating to service delivery and provision of healthcare resources. All expert panel interviews were guided by an interview topic guide (Appendix 3).

4.3.3 Development of a Conceptual Framework

A LRRC-specific conceptual framework of HrQoL was developed by combining inductive (top-down) approach and deductive (bottom up) approaches [225, 262].

- Inductive Content Analysis

An inductive or top down approach was utilised to develop a conceptual framework based upon a systematic review of HrQoL issues in LRRC (Chapter 2). This review identified a number of HrQoL issues associated with LRRC and its management. A second review identified HrQoL issues pertaining to patients undergoing pelvic exenteration. The themes extracted from these two reviews were combined to produce a provisional working conceptual framework consisting of ten broad based domains which included physical impact, psychological impact, social impact, symptoms, finance and occupational impact, relationship with other, communication, body image, sexual function and treatment expectations. The provisional working conceptual framework informed the development of the topic guide for the focus groups.

- Deductive Content Analysis

The provisional conceptual framework informed the subsequent qualitative work. Focus groups were conducted to elicit information pertaining to the impact of LRRC on HrQoL, to define specific

domain components and to clarify and confirm the importance of the identified provisional themes in a group of patients with LRRC. Data obtained from the qualitative focus groups were used to refine and revise the working conceptual framework. This framework was reviewed by an expert panel prior to finalisation.

4.4 Recruitment

4.4.1 Eligibility

Inclusion Criteria

Identified patients were included in the study if the following criteria were fulfilled:

- aged ≥ 18 years
- with an existing resectable LRRC **or**
- surgically treated for a LRRC within the last two years **and**
- able to provide informed written consent to participate **and**
- able to read and write in English

Exclusion Criteria

Patients were excluded from the study in any of the following criteria applied. They:

- have undergone non-surgical palliative treatment of their LRRC
- have cognitive impairment
- are unable to speak/read and/or write English
- are unable to provide informed consent

4.4.2 Patient Recruitment

Patients were identified from a prospectively kept disease register at St James University Hospital, Leeds and The Royal Prince Alfred Hospital, Sydney. Ethical approval was gained from both UK and

Australian sites prior to the commencement of this study. Patients that met the eligibility criteria were approached, informed about the study, and provided with a project information leaflet which included details about the rationale, design and personal implications of the study, and an agreement form to be contacted by the researcher. Following the receipt of the signed agreement form, the researcher contacted the patient, informing them of the time of the focus group.

4.4.3 Baseline Data Collection:

The following data were collected:

- Patients initials and date of birth
- Gender
- Primary Cancer Details (location, neoadjuvant/adjuvant treatments, date of operation, operative and histological detail)
- Mode of detection of LRRC (symptomatic or surveillance)
- Treatment plan of LRRC (pre-operative treatment, operative detail and histological detail, post-operative treatment)
- Current disease status.

4.5 Results

4.5.1 Patient Demographics

Twenty-three patients with operatively managed LRRC between January 2010 and January 2012 consented to participate. Gender specific patient teleconference focus groups were undertaken over a four week period, with a total of 6 focus groups undertaken to achieve saturation. A total of 21 patients participated, 12 male and 9 female patients with a median age at time of interview of 63 years (IQR 50-75). All 3 male focus groups consisted of 4 patients each and all 3 female focus groups consisted of 3 patients each. Median time elapsed between the operation for LRRC and the interview date was 11.7 months (IQR 3.1 -24). Patient demographics are outlined in Table 4.2. Patients were

selected to ensure equal representation of disease subsite, the presence of concurrent metastatic disease and the use of multimodal preoperative treatments (Table 4.2). Median length of the teleconference focus group was 72 minutes (IQR 61-85).

Table 4-2 Patient Demographics

Factor	***Number of Patients***
Median Age	63 (50-75)
Gender	
Male	12
Female	9
Primary Operation Type	
Anterior Resection	15
Abdominoperineal Excision of Rectum	2
Hartmaans Procedure	3
Proctocolectomy	1
Neoadjuvant Treatment – Primary Cancer	
None	13
Chemoradiation	6
Radiotherapy	2
Adjuvant Treatment – Primary Cancer	
None	8
Chemotherapy	12
Chemoradiation	1
Reason for Detection of Recurrence	
Surveillance	14

Symptoms	7
Neoadjuvant Treatment – Recurrent Cancer	
None	6
Chemoradiation	11
Chemotherapy	4
Adjuvant Treatment – Recurrent Cancer	
None	17
Chemotherapy	4
Subsite Location	
Central	7
Anterior	5
Posterior	5
Lateral	4
Operative Procedure for LRRC	
Total Pelvic Exenteration	4
Anterior Pelvic Exenteration	2
Posterior Pelvic Exenteration	1
Excision of recurrent tumour mass	4
Completion proctectomy	5
Ultralow Hartmaans	1
Composite abdominosacral resection	4
LRRC and Metastatic Disease	
Liver	3
Lung	2
None	16

4.5.2 Identified Themes and Conceptual Framework

On scrutiny of the data and the emerging themes, two distinct patterns emerged, the majority of the themes and categories identified addressed the issue of HrQoL, however, a minority, addressed issues relating to healthcare service delivery and utilisation. Saturation of all emerging issues was achieved by the 5th consecutive focus group, with no further issues identified in the final focus group (Table 4.3). Table 4.4 presents a list of quotation relevant to each subdomain.

Table 4-3 Saturation Grid

DOMAINS	FOCUS GROUP 1	FOCUS GROUP 2	FOCUS GROUP 3	FOCUS GROUP 4	FOCUS GROUP 5	FOCUS GROUP 6
Symptoms	Vaginal symptoms Gastrointestinal symptoms Pain Fatigue Urological symptoms Stoma Issues Adaptation of life to symptoms			Locomotor symptoms		
Sexual Function	Practical Issues Gynaecological symptoms	Erectile dysfunction Sexual desire	Stomas interfering with sex			
Psychological Impact	Shock Surprise Anger Self-confidence Self-consciousness	Hope Relief	Change in perceptions Embarrassment Attractiveness and body image			
Role Functioning	Work Housework/General activities Dependence on others	Change in occupational status Finance Leisure activities Hobbies Communication with partner				
Healthcare Services Utilisation and Delivery	Convincing healthcare professionals Hope of Cure Limited Options	Intensity of diagnostic imaging, delays, concerns regarding progression Prolongation of life	Professional communication and support Length of Recovery		Travel	
Future Perspective	Morbidity Restriction Short term plans	Hope	Adjuvant therapies Anxiety regarding appointments and symptoms			

Table 4-4 Illustrative quotes highlighting identified themes

Theme	Illustrative Quote
Symptoms	
Pain	'I had this deadly pain, at the bottom end' 'I've had a pain in my hip'
Lethargy	'I'm tired, I don't have the energy I use to.' 'I haven't got the energy anymore' 'I just can't summon the strength to do something on a regular basis'
Gynaecological symptoms	'my vagina sits flat, everything isn't as it use to be and I've had a few small bleeds'
Urological symptoms	'I'm not able to pass water as energetically as before, if you like, it was starting to get a bit of dribble' 'Its pretty embarrassing when you start to dribble and you can't direct that as well as a stream, and I've wet my legs on more than one occasion' 'I have the symptoms of bladder infections all the time with burning when I pass urine'
Gastrointestinal symptoms	'The rectum still produces lubrication fluid, and if you don't empty that regularly it can be uncomfortable' 'I get discharge from my back passage, it's damp and messy'
Locomotor symptoms	'Well with the wound in my back, i have no mobility its not handy' ' Its the lack of mobility, that can be depressing' ' I can't walk on my crutches, I've got no feeling in my feet'
Sexual Function	
Sexual Intercourse	'I had bleeding and pain during sex. I couldn't have sex because it was just too sore.' 'Other than the fact they took everything out and the sex life is now down the drain' 'The physical side of the marriage, the sex side of things, has ceased... was the second time, more nerves were damaged and obviously I had some more chemotherapy and that was the end of it really.'
Psychological Impact	
Mood	'It was pretty depressing and like i say i've got it again' 'The second time my cancer returned I felt very frustrated, angry, mainly because I thought I'd done all the right things'
Self-efficacy and Dependence	'I find it difficult from my point of view of relying on others and whether you are a burden to them' 'I feel my self-confidence is gone.' 'I do get frustrated at times that i'm not as independent as I use to be'
Appearance and Body Image	'I don't like my body. I don't like all the scars, i don't like having a bag' 'I felt like a body devoid of organs'
Role Functioning	
Work	'I don't get up onto the scaffolding, I get up on the planks and on the ground, I can reach up, so its affected me a little bit, and I'm a little slower than I was' 'I think with the stress of the finances...it makes things worse'
Household Activities	'I use to go to the Saturday market for food shopping, and I can't do

	that anymore.' 'Tasks that need to be done, such as washing the car, cutting the grass or trimming the hedge or whatever it is, you're gasping for breath, for something which you use to take in your stride before, so fatigue, is a major element'
Social	'We still go out to nightclubs and see bands, i don't get up and dance much, socially, its negative now. There is very little social activity now.' 'My activities have changed, I use to go for long walks and kayaking, I don't do that as much, I don't go out as much now.'
Relationships	'That's what kept me going too, talking to neighbours and mates' 'Obviously, it has an impact on my wife, she gets very stressed at times... but, we talk about it very openly.' 'be open about your problem and talk to your family and your mates, otherwise you'll go downhill' 'it's awful for my family, that's the most upsetting thing, that's the impact it has on your family and how they feel.'
Future Perspective	
Disease Re-recurrence	'Lately I've had a pain in my hip, and that concerns me because it could be the cancer coming back, and so I'm in the process of dealing with that' 'Any little ache or pain I think the cancer is coming back, it not there all the time, it's just when I get a pain or symptom that when I think about it'
Further Treatments	'I was having chemo and I wasn't expecting it and everything was going wrong' 'Apart from having my hernia fixed I thought that's all I would need, I didn't think I would need any more surgery than that and I could get on with my life'
Future Plans	'I don't think mine will come back, I'm pretty positive' 'I've been very unconfident that I'll still be alive in 18 months time and we'll see...because things are going wrong' 'Short term; take every day as it comes.'
Healthcare Services Utilisation and Delivery	
Disease Management	'It took a long time, about 6 months for them to figure out what to do, where I'm from they are not equipped to do that sort of surgery.' 'I felt like I kept getting left behind, I ended up having to get the doctors here to push the doctors in Adelaide to get things going.' 'It took a bit of pushing to get it checked out just took a long time to sort it out.' 'The recurrence was detected after several scans; again, it didn't just come in, one single dose as it were.'
Treatment Expectations	'There were difficulties, I ended up with a urostomy and colostomy bag, there were some difficulties in that operation too, and I spent a total of 6 months in hospital.' 'It cured what need to be cured at the time.' 'I viewed and expected my surgery to be curative and that it is absolute cure, I'm just hoping they have fixed me and it doesn't come back and I can have a bit longer before I have to worry about it' 'It took me a long time to recover but in that recovery period I was determined'
Healthcare Professionals	'I chased the information.'

	‘As far as information before the operation was concerned that was adequate, my concern was far more the lack of information afterwards.’ ‘We had trouble in waiting, almost as though they weren’t in communication with the hospital that had initially done the scans and scopes, and we were waiting for quite a long time between having the scans done and getting through to Leeds and working on it, it’s quite a delay’

4.5.2.1 Health Related Quality of Life Themes

4.5.2.1.1 Symptoms

Pain

Patients with LRRC reported some form of pain and discomfort. Common sites of reported pain were abdominal, perineal, back and leg pain. Perineal, back and leg pain was typically, described to be ‘a numb and dead pain’, ‘shooting pain’ or ‘a nerve pain’; these descriptors are commonly associated with neuropathic pain. Abdominal pain was more commonly described to be ‘crampy’ or a ‘dull ache’. Pain is typically described to get worse throughout the day ‘Worse of an evening... My best time is the morning, so I try and do everything I possibly can in the morning’.

Pain caused significant discomfort and interference with activities of daily living ‘I’m careful about lifting, working hard with vacuum cleaner because it makes my muscles ache’ and the ability to assume comfortable positions ‘I still can’t sit comfortably I can’t sit on a sofa or a soft seat’.

Fatigue

Patients complained of feelings of lethargy, malaise and a general lack of energy. This generally led to an inability to carry out tasks, requiring a break or abandonment of the task in the hand. ‘When I would get tired I would sit down and catch my breath’.

Gynaecological Symptoms

Fifty five percent of women reported vaginal symptoms, this included vaginal pain and numbness, bleeding and discharge. These symptoms interfered with daily life, intimacy, body image and social

activities. Women felt they were unable to embark upon sexual and intimate relationships as a consequence of these symptoms, with this causing emotional distress such as anxiety and feelings of self-consciousness. '...because my anatomy is a bit messed up the very thought of having an intimate relationship would bother me and also the thing is having a colostomy, it's something, that I just couldn't envisage myself getting into a relationship'.

Urological Symptoms

Urological symptoms were reported both by men and women. Patients described a range of urological symptoms including urgency, incontinence, dribbling and poor flow with these symptoms causing a significant amount of discomfort. This caused a significant amount of emotional distress and embarrassment, with the avoidance of social situations where a toilet was not easily accessible. Patients stated they had to adapt their lifestyles to accommodate these symptoms with the use and carriage of incontinence pads, the need for urinary catheterisation and the avoidance of public urinals. 'If I sit for too long and I stand up I just pass water. I wet myself quite a lot and I find that embarrassing'.

Gastrointestinal Symptoms

Patients complained of few gastrointestinal symptoms, with the two main symptoms being that of flatulence and rectal discharge. Rectal discharge caused discomfort, embarrassment and required the use of incontinence pads to manage these symptoms; 'Its uncomfortable, it's not huge volume or anything, but it's damp and messy'. The symptoms of flatulence were more easily managed socially through the use of humour; 'if I make a bit of a smell, well that's the price they pay for my company'.

Stoma Related Issues

Approximately 70% of patients included in this study had a stoma (colostomy or urostomy). Patients complained of stoma related issues in the immediate post-operative period, with stomal leakage being the main complaint, however following a period of adjustment, patients adapted to this. Longer term issues related to the stoma, including difficulties engaging in sexual relationships and social activities

due to feelings of embarrassment and emotional distress. Patients described the stoma to be a permanent reminder of their cancer journey. Overall, there was an acceptance of the stoma(s) as all patients felt there was no other alternative 'I don't mind the bag – its either a bag or the box'.

Locomotor Symptoms

Patients with posterior recurrences involving sacral resection reported symptoms of lower limb pain and paraesthesia, which led to impairment in mobility and a restriction in movement, leading to disruption of daily and social activities. 'I have tingling in the bottom of my feet, its like throwing a couple of handfuls of sand in your shoes and then walking around', 'I can't walk on my crutches, I've got no feeling in my feet', ' My wife puts my shoes and socks on because where they cut my legs I can't bend them, I can get them off but I can't get them on'.

4.5.2.1.2 Sexual Function

Sexual function was significantly impaired following operative management of LRRC, with the majority of patients citing a reduction or complete abstinence from sexual intercourse. Reasons cited for this included gynaecological symptoms of vaginal numbness, pain and bleeding, erectile and ejaculatory dysfunction, issues with self-confidence and body image and the practical issues of having a stoma. '...my anatomy is all different and I still have bleeding and that now I guess my body is all different'.

Male patients continued to express feelings of sexual desire, however female patients experiencing gynaecological symptoms had no such feelings. Patients substituted the lack of sexual intercourse for other activities such as kissing and cuddling 'we have a cuddle but there's nothing sexual'. Feelings of guilt and sympathy towards partners were expressed for the lack of a sexual relationship, however,

overall patients felt little adverse impact on their marital relationships. ‘I’ve surprised myself, I thought it would affect me, it’s one of those things you put a lot of importance on, whilst you share that part of a relationship, now it’s been taken away, yes it was a shock at the time, but when you’ve got a relationship as strong as we have’.

4.5.2.1.3 Psychological Impact

Mood

The diagnosis and treatment of LRRC had a significant impact on psychological wellbeing. Patients expressed a range of emotions to their initial diagnosis of LRRC, including surprise, shock, anger and disappointment. Feelings of shock and surprise were more commonly expressed by patients who had their recurrence detected during routine surveillance investigations ‘I was surprised because I was feeling so well and everyone said I looked well. So I was shocked’. Feelings of disappointment and anger were expressed at disease recurrence following the recovery and perceptions of cure after the first operation; ‘I was pretty much devastated....you think you’ve beaten it you see, you’ve had the cancer at first and I had the operation and the chemo, and you just felt so well, and I did everything I could, it was just a massive shock’.

Frustration and feelings of anxiety were commonly expressed during the investigative period when trying to obtain a definitive diagnosis, however this changed to feelings of hope and relief when potentially curative treatment in the form of surgery was offered ‘so, obviously I was really down at that point, but later on my initial surgeon, said he knew a colleague in Leeds, that was Mr Sagar, who said he could operate, so at that point I was elated’.

Patients adopted a positive and hopeful attitude in the peri-operative period, with an emphasis on achieving cure and early recovery. Feelings of frustration were greater when recovery was felt to be prolonged due to on going treatments and when restrictions on daily activity were imposed as a result of recovery; ‘Personally I was fed up because I was having to have dressings all the time, and I was

thinking just hurry up and heal up, and it still hasn't healed up, and we're a year down the line'. Despite these feelings of frustrations during the management of complications patients were grateful for the chance of undergoing potentially curative surgery.

Self-efficacy and Dependence

The loss of independence and the dependence on others due to the impact of disease recurrence and surgery had a huge adverse impact of patients, as the majority of patients had felt they had only just regained their independence and restored their lives to normality prior to being diagnosed with recurrent disease. This often led to feelings of anger, frustration and isolation, and was further exacerbated by societal changes in perception of identity and role functioning. 'I think people regard me with a lot more pity and I don't like that, I don't like people feeling sorry for me'. 'One of the difficult things was at work when the second time, when the cancer came back and I had to go off, they sat me down, and said now in employment law you're classed as disabled.... when someone classifies you as disabled that's a really hard thing to take'. 'They were people in the office looking the other way, or not looking you in the eye and you sort of feel alienated'. Patients felt frustrated that they had to rely on others to carry out normal daily activities such as getting dressed, shopping and socialising, which led to a loss of independence and feelings of being a burden 'I find it difficult from my point of view of relying on others and whether you are a burden to them'.

Appearance and Body Image

Changes in patient perception of body image and appearance were related to physical and psychological aspects of their LRRC treatment. The physical components consisted of the presence of a permanent stoma, multiple wounds with delayed healing, abdominal wall fistulae, abdominal wall hernias, weight loss and loss of sexual organs and sexual function. These physical factors had a significant psychological impact leading to feelings of self-consciousness, lack of self-confidence and embarrassment which often led to social isolation due to voluntary lack of participation in certain

social settings and the non-engagement in potentially new relationships. ‘it’s not very nice to look at is it, when there are that many scars’.

4.5.2.1.4 Role Functioning

Work

Due to the significant physical constraints of re-operative surgery, a number of patients stated a change in occupational status, taking a ‘lesser’ job on with fewer responsibilities and where applicable lighter duties. In some instances, patients have been unable to go back to work and have had to resign or take early retirement. ‘I have renegotiated my contract with my employer, where I’ll work a little bit each week, each day, but I’ll be honest I’m doing very very little at the moment’. These changes are to accommodate symptoms of the disease recurrence or recovery period combined with general symptoms of lethargy and malaise, as well as to accommodate on going adjuvant treatment. There is an obvious financial implication in making such adaptations, which goes onto cause anxiety about the future and long term plans to provide for the family.

The change in occupational identity can have a significant psychological impact, with patients feeling a loss of sense of self when occupational activity ceases or feeling the constant need to prove oneself upon return to work following recovery. ‘I resent my identity been taken away from me, I’ve had to give up work, I worked in a pub, I loved it, but I can’t work now, as I don’t know whether I’m going to need chemo or how I’m going to feel’, ‘I had to make a lot of adjustments but I felt that now, because I’ve had two bouts of this, I constantly have to prove myself that I’m still capable of doing the job and that if I lose that I’ll lose a bit of me really and if I sort of forget something, or I make a mistake, or I make a wrong judgement, I feel very much that the directorship of the company will think she’s had cancer twice, and the whole stigma of it’.

Household Activities

Alongside, changes in occupational activity there is a shift in the type and pattern of household chores and general activities undertaken by patients, with a dependence on spouses and family members in the initial post-operative phases to undertake all household chores, however this reduced with gradual recovery and improvement in post-operative function. Despite, a slow return in undertaking daily chores, patients were reluctant to undertake 'heavier duty' chores such as gardening, heavy lifting or vacuuming for fear of symptoms of pain. The inability to perform such tasks combined with the dependence on others leads to feelings of guilt, frustration and a lack of self-confidence. 'I haven't been able to do everything I wanted to do, and it knocks your confidence, you feel as if, not useless exactly, you feel like you're letting the family and the side down by not doing what you're suppose to do'.

Social

Patients reported a reduction in social and leisure activities following operative intervention, with a very slow and gradual recovery of these activities. The return to participation in these activities is often cited as a positive motivating factor for recovery. Although there is a restoration of leisure activities and hobbies in the post-operative phase, patients tend to adapt these activities a little to match new and lower energy levels. 'I still get onto my motorbike, to ride it, I just don't race much because my reflexes aren't that quick'.

Patients report variable social participation, with certain social situations causing anxiety and embarrassment. This was most relevant when going abroad on holiday and having to potentially expose parts of their bodies and when in public places without easy access to public toilets; these situations caused a great deal of anxiety and made patients feel self-conscious. Patients generally adapted their lifestyles to accommodate social activities to minimise embarrassment and discomfort. 'I'm going on holiday this year, and I'm really frightened to go on holiday', 'I have plenty of pads, I have my little colostomy sets for changing that and I always keep an extra set of pads and panty liners.'

Relationships

Overall, patients felt personal relationships (marital, family, close friends) strengthened during the diagnosis and treatments of their LRRC, with a great emphasis placed on communication, especially, with regards to decision making regarding treatment strategy. The communication between couples helped overcome other changes engendered by their LRRC in their relationships such as intimate and sexual relationships. When patients weren't able to communicate with their partners this caused feelings of sadness and anxiety. However, patients did not disclose all their feelings to their partners or family members for fear of upsetting them and being perceived to having a negative outlook. Feelings of guilt were also expressed by patients when discussing their partners for having put them through cancer a second time round, as well as for adopting a more dependent role and not being able to contribute equally to the household or family. The feeling of dependence extended to all members of the family who helped in the patients care, with associated feelings of guilt and a loss of the sense of self. 'I felt that I had to rely on hubby for everything and so you feel a bit guilty that you're relying on one person'.

4.5.2.1.5 Future Perspective

Disease Re-recurrence

Despite patients undergoing a curative resection for their LRRC, they all expressed anxieties and concerns regarding the potential for disease re-recurrence in the future. Symptoms of complications were often misinterpreted as evidence of disease re-recurrence and therefore, all such symptoms were over-reported to all healthcare professionals and caused a great deal of anxiety. In symptom-free patients, the period of time leading up to follow up appointments and investigations were deemed too anxious and nerve-racking. '...it's still in the back of your mind that it might come back again I try

and put it to the back of my mind, I try and put it out of my mind but it is there but I do get quite wound up when I go for scans and appointments'.

Further Treatments

Patients expressed surprise at the need for further adjuvant treatment in the form of chemotherapy following surgery, however understood, the reasoning behind this and therefore accepted it as part of their treatment package. The need for further adjuvant chemotherapy was deemed to cause social interference and prolonged overall recovery time.

The morbidity associated with LRRC surgery was often underestimated by patients, with expectations expressed of a short post-operative recovery similar to their primary rectal cancer surgery, with frustration expressed at the on going treatments required for slow healing wounds, fistula management, abdominal wall hernias and recurrent episodes of intestinal obstruction. 'I've been in about 8 times, with various problems, the colostomy bag since 2004, is permanent obviously, it has had 4 different locations, 2 different operations for hernias', 'I'm nowhere near recovered, I'm 50% there but I've been having my wound dressed for the last 12 months'.

Most patients learnt to adapt and accommodate symptoms arising as a result of post-operative morbidity, despite some restrictions imposed upon social and daily activities, especially, with regards to regular wound management.

Future Plans

All patients regarded surgery as a prolongation of their lives, irrespective of whether the surgery was curative or palliative, and viewed the future to be hopeful and optimistic, However, despite, this overall, positive attitude, patients made very short term plans, adopting an attitude of living on a day-to-day basis as opposed to making any committed long term future plans. This was due to the potential fear of failure, and as they had experienced this once before with their primary rectal cancer. 'One day at a time, I don't know, if I'll have a long future or not'.

4.5.2.2 Themes Identified Related to Health Services Delivery and Utilisation

4.5.2.2.1 Healthcare Services

Disease Management

Patients reported difficulties in obtaining a definitive diagnosis of their LRRC, especially, when they were experiencing symptoms, as they felt an intuitive sense of disease recurrence, 'the illness had come back, it had taken me quite a few months for me to persuade the surgeon here that something was wrong; I kept telling him that something wasn't right', 'think when you find you've got it again, it's almost like you know you've got it and you dread it again', 'really getting some discomfort, when to see my chemo specialist, who said, no, no its not related to that, it's probably just a trapped nerve, but I insisted on having some bloods taken which revealed there was a problem and I was scanned and it proved the tumour had returned in the sacral area'. Where there was an insistence on the patients' part to have these symptoms further investigated by their healthcare professional, this occasionally led to the breakdown of the doctor-patient relationship and feelings of frustration.

The investigative pathway for the detection of LRRC was felt to be intense and often induced feelings of anxiety and 'not knowing', which led to considerable emotional distress both for the patient and their partners. This was exacerbated by perceived delays in obtaining the diagnosis and potential referral delays between general and specialist services, which led to anxiety and concerns regarding disease progression and spread. This led to a significant degree of interference with social activities, with the cancellation of holidays and avoidance of certain social situations in case further investigations or appointments were made at short notice. 'The recurrence was detected after several scans; again, it didn't just come in one single dose as it were.... It was basically, the lead up of several scans and x-rays, it was becoming obvious, so by the time, they'd announced the recurrence, you already knew that by the sheer volume of the intensity of the scanning that was going on.', 'I then had another CT scan and another MRI scan, and then went to Nottingham and had the PET scan and still no-one knew what was going on', 'We felt that there was a long delay in finding out that there might be something and actually deciding that there was something, we were a long while, in no man's land,

not knowing one way or the other', 'It's that delay, the month without any treatment you don't know whether things might be growing or spreading'.

Patients reported difficulties in travelling to the specialist centres for diagnostic purposes, treatment and follow up, as if the local and specialist hospitals were over a great distance the physical act of travelling was often uncomfortable due to symptoms of pain. However despite this patients preferred to have their on going post-operative follow up and the management of complications at the specialist centre, irrespective of the distance required to travel as they had more confidence in the expertise of the specialist centres. 'If there was a problem the doctors here (Adelaide) weren't quite sure because it wasn't their expertise', 'I'm just glad I went back to Sydney for my check up and nowhere else because it (third recurrence) might not have been picked up earlier'.

Treatment Expectations

Patients expressed feelings of' 'hope' and 'relief' upon being offered operative management of their LRRC, with a view that this would 'prolong' their lives, irrespective of the success of the surgery; 'I thought great, I'm not looking forward to the operation but here's hope again', 'it was cutting edge surgery, but my view was that it was going to improve my longevity I'll buy into that and I have done and I wouldn't change it', '400 people diagnosed with similar to me, with half a dozen operated on and I was one of the lucky ones to be operated on but in the past there just wasn't the technology. I was getting desperate let's put it that way, if there's an opportunity to increase ones longevity'.

Patients stated they had limited treatment options, with surgery being the only curative option, with chemotherapy being reserved for palliative treatment only, 'I just thought that palliative care, was just a slow way of going, if you like, or whatever, but at least with an operation there was a chance we could still beat it'. Patients expressed feelings of having 'no other alternative', 'as one said earlier on its the op or the box, you don't have a real choice in the matter'.

Patients' treatment expectations were intrinsically linked with their future goals in life and their psychological well being. When given the option of potential life saving surgery patients outlook on life improved and gave them hope for a prolonged future, thus minimising some of the psychological distress associated with the recurrent cancer. This shifted their psychological outlook from being negative to positive, and thus impacted on their overall wellbeing.

Patients envisaged a quicker post-operative recovery and did not expect potentially long hospital stays. The process of recovery impacted upon physical function, restricting daily activities and prolonging the return to work, this was associated with a greater dependence others, which often led to feelings of 'frustration'.

Healthcare Professionals

Patients expressed variable confidence in the decision-making and disease management of their surgeon, with less confidence in their primary surgeon compared to their specialist surgeon, this was most pronounced when patients had difficulty in obtaining a definitive diagnosis of their recurrent disease. However, all patients expressed complete confidence in their specialist surgeon and were guided by their expertise in the management of their LRRC.

Patients felt occasionally there was ineffective communication between healthcare professionals regarding management decisions and this impacted adversely upon their care, which led to feelings of anxiety and worry. Despite this perception, patients felt their own communication with healthcare professionals was good, with an adequate amount of information given regarding the management strategy combined with all associated risks. This exchange of communication led to an alleviation of anxieties and put patients at ease; 'I was made very comfortable and I was very confident with his capabilities and I knew I was in a safe pair of hands'.

Patients felt upon discharge there was a lack of psychological support available from British and Australian healthcare services, as a result, patient sought such support from external services, such as

‘The Colostomy Association’ and ‘The Holistic Centre’. Patients valued this support as it meant the disclosure of thoughts and feelings they could not share with their family, with this disclosure leading to the alleviation of some emotional and psychological distress. Furthermore, patients felt they could not make such disclosures with their doctors, preferring to discuss physical issues alone. ‘I like people in a professional way to talk really’, ‘I think should it be part and parcel of the recurrence of my cancer.’, ‘I went for quite a few months, and there were things I could say to them that I couldn’t tell my family’.

4.5.3 Patterns of Association

A cross analysis of the data was undertaken to identify any association between patient and disease factors (age, gender, method of detection of recurrent disease, pre-operative and post-operative treatments, subsite location of disease recurrence, margin status and current disease status) and HrQoL issues. For all the factors, the reported HrQoL issues were the largely the same for all patient types. Patients with posterior and lateral recurrences complained of pain and locomotor symptoms more frequently than patients with central and anterior disease. Conversely, patients with central and anterior recurrences complained of gastrointestinal, urological and gynaecological symptoms more frequently than patients with posterior or lateral disease. There were no differences in the HrQoL issues expressed between patients in the UK and Australia, with both sites being similar in terms of health services infrastructure, with patients being referred from generic to specialist services. These similarities in infrastructure led to similar issues being reported by both population groups such as lack of referral services, frustration at seeking diagnosis and treatment and long travel in both

geographical regions.

4.5.4 Expert Panel Review

The expert panel group consisted of a clinical team of 6 surgeons (3 British, 3 Australian), 2 clinical oncologists and 2 colorectal nurse specialists. In addition to this, the executive and deputy executive directors of the Surgical Outcomes Research Centre, Sydney, with backgrounds in public health and epidemiology and clinical psychology participated in the expert panel interviews.

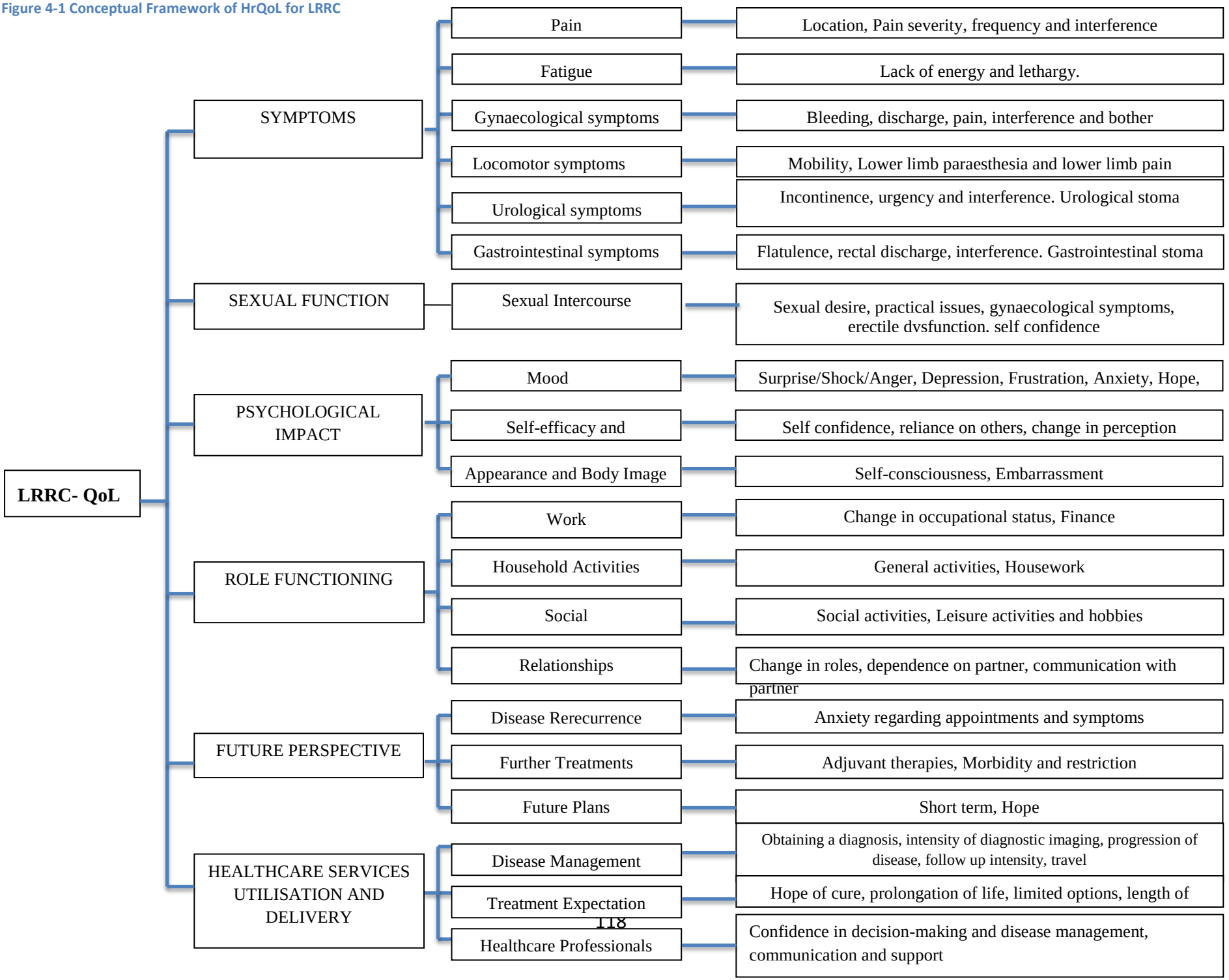
The panel generally agreed that clinically relevant themes had been identified through the patient focus groups, with complete agreement on the inclusion of the first 5 domains (symptoms, sexual function, psychological impact, role functioning and future perspective). The expert panel suggested the identified subdomain of *Stoma Related Issues* should be divided into a gastrointestinal stoma and a urostomy and be incorporated into the subdomains of gastrointestinal symptoms and urological symptoms, as this will help distinguish patients based on their stoma type and may potentially provide discriminatory HrQoL data in these subgroups of patients.

Opinion was divided amongst the expert panel regarding the final domain of healthcare services, as some experts felt this domain concentrated on the provision of healthcare resources and therefore would provide information on the infrastructure and delivery of health services and not HrQoL. Conversely, other experts felt that this domain addressed an important issue regarding the delivery of health services and its potential impact on patients overall well being and HrQoL, and therefore will be useful in informing future healthcare policy. All the experts agreed this domain addresses important issues relevant to patients with LRRC, however opinion was divided on its incorporation into a conceptual framework addressing HrQoL. There was some discussion of the using this domain as a module to assess current health services and to monitor changes in healthcare services as an exercise to inform future healthcare policies.

4.5.5 Finalised Conceptual Framework

The themes extracted from the two systematic reviews n HrQoL in LRRC and PE were integrated with the analysis. The final LRRC-specific HrQoL framework includes six domains and 21 sub-domains (Figure 4.1.)

Figure 4-1 Conceptual Framework of HrQoL for LRRC



4.6 Discussion

This is the first qualitative study undertaken in patients with LRRC to examine HrQoL issues relevant to this cohort of patients. The findings of this study have been used to devise a conceptual framework which will inform the overall development of a PROM of HrQoL in this patient population. This study identified two patterns of issues relevant to patients with LRRC, the first being relevant to overall HrQoL and the second relevant to healthcare service delivery and utilisation. A total of six domains or constructs were identified by this study. A number of constructs identified in this study are similar to HrQoL domains in established PRO measures for primary rectal cancer, however a number of LRRC-specific components were also identified. The symptoms experienced by this cohort were wide ranging and affected a range of systems and were not only gastrointestinal specific as seen in primary rectal cancer patients. In addition, several other components emerged that have not been previously identified, including that of 'future perspective' including 'disease re-recurrence', 'further treatments' and 'future plans'.

Previous research has used established quantitative measures for primary rectal cancer to ascertain the impact of LRRC on HrQoL. These studies have reported negative impacts on HrQoL in terms of physical functioning [185, 187, 190, 192], psychological and emotional function [185], social function [185, 190, 193], occupational role [190, 193], as well as a variety of symptoms. Consistent with the findings of these studies, our study identifies these constructs. Previous qualitative work in advanced rectal cancer requiring an extended pelvic resection identified themes beyond those identified through quantitative measures. These themes included 'the life changing impact of surgery [263], 'patient satisfaction with immediate care in hospital [263], 'significant chronic pain related to sacrectomy [263], 'patients need for additional information regarding long-term recovery [263], 'patient gratitude to be alive [263]. 'all that is important is your health [194], 'limited options [194], 'believe in your own intuitive sense of self [194], 'unanticipated morbidity [194], 'mistaken perception of cure [194] and 'appropriate and timely information needed [264]. Our study reflects these themes, and

incorporates the themes identified by previous quantitative and qualitative work, which has been further supplemented by the perceptions of patients who have undergone surgery for LRRC. Thus ensuring the final conceptual framework is reflective of patient opinion with regards to important and relevant issues

Differences were explored between patients in terms of patient and disease factors as well as location (UK versus Australia). No major differences were observed between the subgroups apart from in terms of symptoms, with patients with anterior and central recurrences complaining of more gastrointestinal, urological and gynaecological symptoms than patients with lateral and posterior recurrences. This latter group of patients complained more of pain and locomotor symptoms. These findings are in keeping with previous work [8, 69] and can be explained due to the pattern of organ invasion by the disease recurrence, with anterior and central recurrences more likely to invade the neorectum/rectal stump and urogenital organs leading to a variety of symptoms including rectal bleeding and discharge, vaginal symptoms and urinary symptoms. Similarly, posterior and lateral recurrences are more likely to invade the bony pelvis and the pelvic neural plexus leading to symptoms of neuropathic pain and lower limb dysfunction including paraesthesia and a reduction in mobility. However, despite these observed differences there were no differences between subsite location of LRRC and sexual function, healthcare services, psychological impact, role functioning and future perspective. More importantly, no differences were observed between patients in the UK and the Australia, thus confirming that the issues identified by this study are universal to all patients irrespective of the geographical location where their LRRC disease is managed.

This is the first time issues regarding the provision of healthcare services have been examined from a patient perspective in this cohort of patients, as previous works have concentrated on the provision of services from a healthcare providers perspective alone [265]. Due to the lack of healthcare providers offering a dedicated service in the surgical management of LRRC, there are often potential delays in

referrals and appropriate radiological staging of disease to ascertain suitability for surgical resection, coupled with occasional ineffective communication between primary and specialist teams. These patient perceptions can have a negative impact on HrQoL, especially psychologically, with feelings of frustration, anxiety and worry expressed. Similar themes revolving around the provision of health services have been previously identified through qualitative methodology by Davidge [263] and Wright et al [194] in patients with advanced primary rectal cancer requiring an extended pelvic resection. The themes identified by these authors revolve around the need for adequate communication and information from healthcare professionals in a timely and appropriate manner and the satisfaction with post-operative management.

HrQoL instruments are used in a variety of ways including monitoring an individual patients clinical response to a treatment or intervention, as primary or secondary endpoints in Phase I-III trials and as an outcome measure in health services research [266-268]. The modular system utilised by the EORTC and FACIT groups enables the use of questionnaires in their entirety or partially using only the relevant subscales of interest [267]. A similar approach could be incorporated into the LRRC-QoL, utilising each subdomain as required dependent on the study outcomes and measurement points. This will be most relevant to the domain of 'Healthcare Services' as the expert panel could not agree on its inclusion into the main body of the conceptual framework due to disagreements on the measurement properties of this domain as a measure of HrQoL or provision of adequate health services. However, the qualitative data obtained from patients suggests the provision of health services had an impact on psychological well being, and therefore the inclusion of this domain may provide important information and may potentially impact other aspects of HrQoL measured by the LRRC-QoL. Despite the disagreements on inclusion of this domain all members of the expert panel acknowledged this domain was important, therefore a pragmatic decision was made to incorporate it into the main conceptual framework. The LRRC-QoL should be used in a modular fashion and therefore this domain could be included/excluded in future studies as deemed relevant.

Qualitative data can be generated and collected using two types of methods; through the use of interviews or through focus groups. Both have pros and cons, with focus groups identifying ‘a range of experiences and perspectives’, whilst individual interviews offer in-depth exploration. Focus groups enable participants to react to and build on the comments made by other members of the group, yielding opinions and experiences that may not surface during individual interviews [269]. For the purposes of our study, given the scattered geographical location of patients and the practical constraints of assembling a group together, a pragmatic decision was taken to undertake a series of teleconference focus groups consisting of 3-4 patients each. Our focus groups were single sex, this was to promote patient comfort when discussing sensitive issues such as sexual function and body image, thus providing data which was rich and robust and therefore able to support content validity. Criticisms of teleconference focus groups include the lack of nonverbal communication, which might reduce the richness of the qualitative data and the difficultly in managing group interaction [270]. Despite, these criticisms, teleconference focus group participants appear to be more willing to discuss experiences of a sensitive or personal nature due to the visual anonymity afforded by this medium [271, 272]. Furthermore, recent evidence has found there is little difference in the type of data obtained from face-to-face focus groups and telephone focus groups [272].

One of the potential difficulties in conducting qualitative research is the ‘researcher effect’[273]. The role and position of the researcher can potentially have an impact on the behaviour of the participants. It is well known that participants can behave differently with different researchers. Furthermore, there is the additional issue of researcher bias, with researchers potentially observing behaviours and interpreting findings in view of their own bias. With regards to this study, it is possible that patients may have over reported issues regarding symptoms and under reported more personal and sensitive issues such as sexual function and psychological function. It is possible patients may have placed more emphasis on surgical treatments and reported the consequences of surgery in a more positive light given my clinical role as a surgical trainee. This may have had an impact on themes extracted within this study. To overcome this, it would’ve been ideal to have additional focus groups facilitated by a qualitative researcher with a non-clinical background. This may have potentially lead to some

differences in the themes reported and may have potentially provided a 'richer' data set. However, this was not feasible due to logistical and practical issues. With regards to reporting and observing behaviours and issues in accordance with my own bias, all the teleconferences were recorded and transcribed verbatim and coded by myself and a qualitative researcher. This minimised the potential of researcher bias as all reported issues were appropriately recorded, transcribed and reviewed.

4.7 Conclusion

This study provides qualitative evidence for HrQoL outcomes that are important for patients with LRRC across two geographical regions. Themes extracted from this study have been combined with themes extracted from the current evidence base in this cohort of patients, and have been operationalisation into a conceptual framework. This framework will provide the basis for the development of a new LRRC-specific PROM of HrQoL.

5 Chapter 5 - Systematic Review of Patient Reported Outcome Instruments for Rectal Cancer

5.1 Introduction

The growing emphasis on the integration of patient reported outcomes with clinical outcomes has led to the development and availability of a number of PROMs [88]. To draw valid and robust conclusions from PROs, they must be captured and measured in a standardised manner using measures that demonstrate sufficiently robust measurement properties. PROMs must adhere to a set of minimum standards prior to their use in patient-centred outcomes research and comparative effectiveness research. A number of guidelines exist to guide these standards including guidance from Food and Drug Agency [89], the 2002 Medical Outcomes Trust guidelines [255], the COnsensus-based Standards for the selection of health Measurement Instruments [274-276], the European Organisation for Research and Treatment of Cancer [277] guidelines, the Functional Assessment of Chronic Illness Therapy (FACIT) approach [278] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force recommendation documents [256, 279-281]. These guidelines were recently incorporated with expert opinion by International Society for Quality of Life Research (ISOQOL) to establish a minimum measurement standard to promote the appropriate use of PROMS [282].

Data obtained from PROMs is only valid and meaningful if it has been obtained in an appropriate manner in the intended population in which the PROM has been developed. A review of HrQoL outcomes in LRRC revealed a number of PROMs which had been used to capture this data (Chapter 2). However, the majority of PROMs used to measure HrQoL in this cohort were developed specifically for the study as an ad hoc measure or were developed to measure HrQoL in primary colorectal cancer. The aim of this study was to identify and assess PROMs developed and validated for use in primary rectal cancer and to assess their applicability to measuring PROMs data in LRRC by conducting a domain and subdomain level analysis to identify overlapping constructs.

5.2 Aims

The aims of this review were:

- To identify HrQoL PROMs developed and validated for primary rectal cancer
- To assess identified PROMs against ISOQOL minimum measurement standards recommendations
- To assess the existing PROMs content against the LRRC-specific HrQoL conceptual framework

5.3 Methodology

This systematic review was conducted according to a pre-specified protocol based on guidance from the Centre for Reviews and Dissemination [219] and the Cochrane Handbook [220]. The review is reported in line with the PRISMA statement [221].

5.3.1 Literature Search

Systematic searches of the literature were conducted in Medline, EMbase, Science Citation Index, Ovid Evidence-Based Medicine databases, PychoINFO and Health and Psychosocial Instruments using the following search string ‘rectal cancer’ or ‘rectal neoplasm’ and ‘patient reported outcome’ or ‘questionnaire’ or ‘instrument’ or ‘measure’ or ‘scale’ or ‘index’. For the appraisal of psychometric and operational performance of the measures identified a second search strategy was devised using the following search string ‘validation’ or ‘validity’ or ‘reliable’ or ‘reliability’ or ‘responsiveness’ or ‘responsive’ or ‘internal consistency’ or ‘psychometric properties’.

5.3.2 Study Inclusion Criteria

All instruments included in the review were PROMs which measured rectal cancer related quality of life and/or bowel function that had undergone development and validation in colorectal oncology patients; measures which did not undergo validation i.e. ad hoc instruments were excluded. The following studies were excluded: studies of health-related quality of life instruments, studies of instruments related to colonic cancer alone; studies of instruments that are used in the paediatric population.

5.3.3 Data Extraction and Analysis

Extraction of data for all selected studies was conducted by one reviewer (D.P.H). The accuracy of the extracted data was verified by a second reviewer (B.G). Data were analysed for three broad categories including instrument development and content validity, domain and subdomain level content analysis.

- *Instrument Development and Content Validity*

The following data were extracted for the evaluation of instrument development and content validity: objectives of each questionnaire, characteristics of intended patient population and patient population involved in the questionnaire development, method of item generation, process used for conducting patient qualitative data and methods used to evaluate the draft questionnaire.

Psychometric properties of all identified PROMs were evaluated including reliability (the extent to which the instrument is free from random error), validity (the extent to which the instrument measures what it purports to measure) and responsiveness (the ability of the instrument to detect changes over a period of time) (Table 5.1).

The ISOQOL recommendations on the minimum standards for the design of a PROM for use in clinical research is the most up to date guidance in this field and incorporates the guidance from a number of previously established guidelines [283]. The ISOQOL guideline outlines 6 desirable

standards PROMS should adhere to including 1) A conceptual and measurement model, 2) Reliability, 3) Validity, 4) Interpretability of Scores, 5) Translation of the PRO measure and 6) Patient and Investigator Burden (Table 5.2). It was therefore deemed appropriate that adherence to these guidelines should be determined for each of the identified PROMs to assess whether the PROM was developed in a sufficiently robust methodological manner.

- *Domain and Subdomain Level Content Analysis*

To identify the extent to which identified PROMs covered the LRRC-specific framework a domain and sub-domain level content analysis was undertaken. This identified the number of PROM domains and sub-domains that mapped onto the LRRC-specific conceptual framework. Where names differed from those in the LRRC-specific conceptual framework item content was analysed for relevance and compared against the LRRC-specific domain and sub-domain content to determine consistency irrespective of different labelling.

Table 5-1 Assessment of Psychometric Properties of PROMS

Measure	*Definition*	*Assessment Measure*	*Interpretation of Scores*
Convergent Validity	Measures of constructs that are theoretically related.	Pearson's Product Moment Correlation (r).	>0.60 strong correlation, 0.30-0.60 moderate correlation, <0.30 low correlation
Divergent Validity	Measures of constructs that are theoretically unrelated.	Pearson's Product Moment Correlation (r).	>0.60 strong correlation, 0.30-0.60 moderate correlation, <0.30 low correlation
Internal Consistency	Measure of inter-relational properties of all items within a domain.	Cronbach's α	>0.70 supports internal consistency
Test-Retest Reliability	Stability of scores over time when no change is expected in the concept of interest.	Intraclass Correlation Coefficient	>0.70 supports test-retest reliability
Known Groups Validity	Extent to which the instrument can discriminate between groups that are known to differ on the variables being measured.	Effect size	>0.80 large change, 0.50-0.79 moderate change, 0.2-0.49 small change
		Score change statistics	Statistically significant differences in score
Responsiveness	Ability to detect change over time	Effect size	>0.80 large change, 0.50-0.79 moderate change, 0.2-0.49 small change
		Score change statistics	Statistically significant differences in score

Table 5-2 ISOQOL Recommendations for Minimum Standards for PROMS

Recommendation	***Definition***
Conceptual and Measurement Model	A PRO measure should have documentation defining and describing the concept(s) included and the intended population(s) for use. In addition, there should be documentation of how the concept(s) are organised into a measurement model, including evidence for the dimensionality of the measure, how items relate to each measured concept, and the relationship among concepts included in the PRO measure.
Reliability	The reliability of a PRO measure should preferably be at or above 0.70 for group level comparisons, but may be lower if appropriately justified. Reliability can be estimated using a variety of methods including internal consistency reliability, test-retest reliability, or item-response theory. Each method should be justified.
Validity	
Content Validity	A PRO measure should have evidence supporting its content validity, including evidence that patients and experts consider the content of the PRO measure relevant and comprehensive for the concept, population and the aim of the measurement application. This includes documentation of as follows: (1) qualitative and/or quantitative methods used to solicit and confirm attributes in the evaluation (e.g. race/ethnicity, culture, age, gender, socio-economic status, literacy level) with an emphasis on similarities or differences with respect to the target population; and (3) justification for the recall period for the measurement application.
Construct Validity	A PRO measure should have evidence supporting its construct validity, including documentation of empirical evidence of changes in scores consistent with predefined hypotheses regarding changes in the measured PRO in the target population for the research application.
Responsiveness	A PRO measure for use in a longitudinal research study should have evidence of responsiveness, including empirical evidence of changes in scores consistent with

	predefined hypotheses regarding changes in the measured PRO in the target population for the research application.
Interpretability of Scores	A PRO measure should have documentation to support interpretation of scores including what low and high scores represent for the measured concept.
Translation of the PRO	A PRO measure translated to one or more languages should have documentation of the methods used to translate and evaluate the PRO measure in each language. Studies should at least include evidence from qualitative methods (e.g. cognitive testing) to evaluate the translations.
Patient and Investigator Burden	A PRO measure must not be overly burdensome for patients or investigators. The length of the PRO measure should be considered in the context of other PRO measures included in the assessment, the frequency of the PRO data collection and the characteristics of the study population. The literacy demand of the items in the PRO measure should usually be at a 6th grade education level or lower (i.e. 12 year old or lower); however, it should be appropriately justified for the context of the proposed application.

5.4 Results

A total of 135 articles were identified, which identified 114 PROMs. On application of the inclusion and exclusion criteria, 105 PROMs were eliminated, of which 39 were generic measures, 30 were ad hoc questionnaires, 7 questionnaires were validated for urological conditions, 13 were for psychological well-being, 7 were for assessment of sexual function and 9 were for the assessment of faecal incontinence. Nine measures fulfilled the eligibility criteria, including two core measures with colorectal specific supplementary measures; European Organisation for Research and Treatment of Cancer QLQ-C30 (EORCT QLQ-C30) and the Functional Assessment of Cancer Therapy – General (FACT-G) and 7 disease specific measures. All of the identified measures were developed and validated for use in primary rectal cancer. There were no identified measures which were developed specifically for patients with LRRC

5.4.1 Identified PROMS

EORTC QLQ-C30, EORTC CR38 and EORTC CR29

The EORTC has adopted a modular measurement approach to the assessment of QoL in cancer patients. The EORTC QLQ-C30 is a second generation core questionnaire following the modification of the original EORTC QLQ-C36 [284]. This core measure encompasses a number of QoL issues relevant to a broad range of oncology patients. The QLQ-C30 has demonstrable psychometric properties, with adequate reliability, validity and responsiveness [284]. A number of modules exist to supplement this core measure to assess specific QoL issues relevant to subset cancer populations. The EORTC QLQ-CR38 was designed to supplement the EORTC QLQ-C30 for colorectal cancer patients receiving a range of treatments, including surgery, radiotherapy and chemotherapy [145]. It consists of 38 items measuring body image, sexuality, micturition problems, symptoms in the gastrointestinal tract, chemotherapy-related side effects, problems with defaecation, stoma-related problems, and male and female sexual problems. To reflect the evolving management of primary colorectal cancer, this module was updated in 2007, which led to the development of the EORTC QLQ-CR29 [144, 285]. This consists of 29 items making up 6 domains of micturition problems, abdominal and pelvic pain, defaecation problems, faecal incontinence, anxiety and body image and 11 single items. Both the EORTC QLQ-CR38 and QLQ-CR29 display acceptable psychometric properties[145] [285].

FACT-G and FACT-C

The Functional Assessment of Chronic Illness Therapy Measurement measures QoL in patients with cancer and chronic illness. There is a general version of the questionnaire, the FACT-G, which is administered to all patients and provides a common framework. In addition to this a number of modules exist, which are disease, symptom or treatment specific, including one for primary colorectal cancer (FACT-C). The FACT-G consists of 5 Domains; Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being and Relationship with Doctor [286]. This measure has

been validated in a large sample size of patients with breast, lung and colorectal cancer, with acceptable psychometric properties [286]. The FACT-C retains four of the five subscales of the FACT-G questionnaire (Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being) with 9 additional items comprising the Colorectal Cancer Subscale, it has been widely validated and demonstrates acceptable psychometric properties [143].

City of Hope Quality of Life-Ostomy Questionnaire

The City of Hope Quality of Life-Ostomy questionnaire is a disease-specific measure to assess HrQoL in patients with a stoma, irrespective of the pathology. This PROM was developed using patients with a stoma as a result of a wide variety of diseases including colorectal malignancy, gynaecological malignancy, diverticulitis and other diagnoses [287]. It consists of a total of 90 items across 4 domains of Physical Well-Being, Social Well-Being, Psychological Well-Being and Spiritual Well-Being,

Stoma-QoL Questionnaire

The Stoma-QoL questionnaire is a disease-specific measure used to assess HrQoL in patients with a colostomy or ileostomy due to a variety of benign and malignant diseases [288]. It consists of 4 domains of sleep, sexual activity, relations to family and close friends and social relations to others than family and friends. The questionnaire is available in English, French, German, Spanish and Danish, with confirmation of cross-cultural validity. The questionnaire demonstrates good internal consistency reliability with a calculated Crombachs α of 0.92 and a high test-retest reliability with a Spearman's correlation coefficient of >0.88 [288].

Stoma Quality of Life Scale (SQOLS)

The SQOLS questionnaire was developed to assess HrQoL in patients with a colostomy or ileostomy, irrespective of the permanence of the stoma and underlying disease pathology. The questionnaire consists of 21 items covering three domains of work/social function, sexuality/body image and stoma function [289]. The SQOLS demonstrated adequate test-retest reproducibility with intraclass coefficients of 0.75-0.93 and acceptable internal consistency reliability with Cronbachs coefficient of 0.72-0.89 [289]. The scales were capable of discriminating between patients with worse and better QoL after stoma formation and appropriately correlated with the Physical and Mental Health scales of the SF-12 questionnaire [289].

MSKCC Bowel Function Instrument

The MSKCC Bowel Function Instrument is a disease-specific and surgery-specific questionnaire for patients undergoing sphincter-preserving surgery for Stage I-III rectal cancer[290]. The questionnaire consists of 3 domains Frequency, Dietary, Urgency/Soiling and 4 individual items. The questionnaire demonstrates adequate test-retest reliability with Pearson correlation coefficients of 0.62-0.87[290]. The domains correlated appropriately with EORTC QLQ-C30, EORTC QLQ CR38 and Faecal Incontinence Quality of Life (FIQL) scores[290]. The scales were able to significantly discriminate between radiation treatment groups, type of surgery and type of anastomosis and quality of life.

5.4.2 Development of PROMs

All 9 PROMs included in this review documented the operational and psychometric processes of the PROM in question, with clear objectives of the purpose of the questionnaire and its target population (Table 5.3 and 5.4). The use of qualitative data from patients for item generation, either through focus groups or interviews is documented in 7 studies [143-145, 285-290]. This is supplemented by further

data from literature reviews and an expert clinical panel in 6 studies [143, 144, 285-287, 289, 290]. Prior to psychometric testing a draft questionnaire was evaluated by patients and/or an expert clinical panel in 7 studies [143-145, 285, 287, 288, 290].

Eight studies employed the Classical Test Theory in assessing the psychometric properties of the PROM in question[143, 145, 284-287, 289, 290]. Prieto et al utilised the Classical Test Theory and Rasch analysis when assessing the psychometric properties of the Stoma-QoL [288]. All studies commented on the population in which the validation study was conducted.

Adherence to the ISOQOL minimum standards recommendations were between 50-100%, with 4 PROMS (EORTC QLQ-CR38, EORTC QLQ-CR29, FACT-G and FACT-C) fulfilling all the requirements (Table 5.5). The areas of the ISOQOL recommendations which demonstrated a lack of compliance included measuring responsiveness, translation of PROMs and documentation of patient and investigator burden.

Table 5-3 Psychometric and Operational Properties of Identified PROMS

Instrument	Author Year	Objective	Domains	Scale	No of Items	Intended Patient Population	Patient population used in questionnaire development	Item Generation	Patient Qualitative Interviews and Focus Groups	Draft Questionnaire Evaluation	Patient Cognitive Interviews
City of Hope Quality of Life -Ostomy Questionnaire	Grant/ 2004	Development and validation of an instrument to assess QoL in patients with a stoma.	4 Domains: Physical Well-Being, Social Well-Being, Psychological Well-Being, Spiritual Well-Being	10 point Likert Scale	90	Patients with a stoma	Patients with a stoma with colorectal cancer, gynaecological cancer, diverticular disease or other diagnoses.	Literature review with input from patients and a clinical panel	Interviews and focus groups	Assessed by a clinical panel.	NR
EORTC QLQ-C30	Aaronson /1993[284]	Development of a cancer-specific questionnaire to measure QoL.	9 Domains: Physical, Role, Cognitive, Emotional, Social, Fatigue, Pain, Nausea and Vomiting, Global Health Status and Quality of Life	4 point Likert Scale	30	Cancer patients	NR	NR	NR	NR	NR
EORTC QLQ-CR29	Gujral/ 2007 [144] and Whistance/ 2009 [285]	Update and improve the QLQ-CR38 module and prepare a module that could be validated internationally for use in clinical trials in colorectal cancer	6 Domains: Micturition problems, Abdominal and pelvic pain, Defaecation problems, Faecal incontinence, Anxiety, Body Image	4 point Likert Scale	29	Colorectal cancer patients Stage I-IV	Colorectal cancer patients Stage I-IV	Literature review combined with patient interviews.	Semi-structured interviews	Patients and clinical panel	Cognitive interviews

EORTC QLQ-CR38	Sprangers/ 1999[145]	Construction of a colorectal cancer-specific questionnaire module to be used in conjunction with EORTC QLQ-C30 for assessing QoL.	9 Domains: Body Image, Sexuality, Micturition problems, Symptoms in the gastrointestinal tract, chemotherapy-related side effects, problems with defaecation, stoma-related problems, male and female sexual problems.	4 point Likert Scale	38	Colorectal cancer patients Stage I-IV	Colorectal cancer patients Stage I-IV	Literature review with input from a clinical panel	NR	Patients	Cognitive interviews
FACT-C	Ward/1999 **[143]**	Development of a measure of specific concerns or problems related to quality of life in colorectal cancer patients.	5 Domains: Physical, Functional, Social/Family, Emotional, Colorectal Cancer Subscale	5 point Likert Scale	36	Patients with colorectal cancer in clinical practice or clinical trials	Patients with Stage I-IV colorectal cancer	Literature review with input from patients and a clinical panel	Structured Interviews	Assessed by 30 colorectal cancer patients for relevance and importance	NR
FACT-G	Cella/1993 [286]	Development and validation of a core measure of QoL in cancer patients.	5 Domains: Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being, Relationship with Doctor	5 point Likert Scale	28	Cancer patients	Breast, lung and colorectal cancer patients	Interviews with patients and clinicians	Semi-structured interviews	Patients and clinical panel	NR

MSKCC Bowel Function Instrument	Temple/ 2005 [290]	Development and validation of an instrument to assess bowel function in patients who had undergone sphincter-preserving surgery for rectal cancer.	3 Domains: Frequency, Dietary, Urgency/Soiling and 4 individual items	5 point Likert Scale	18	Patients following sphincter preserving surgery for rectal cancer	Patients with Stage I-III Rectal cancer undergoing sphincter preserving surgery	Literature review with input from patients and a clinical panel	Semi-structured interviews	Assessed by patients for relevance, importance and wording.	NR
Stoma Quality of Life Scale (SQOLS)	Baxter/ 2006 [289]	Development of an instrument to measure QoL in patients with a stoma.	3 Domains: Work/Social Function, Sexuality/Body Image, Stoma Function	5 point Likert Scale	21	Patients with a stoma	Patients with colostomies or ileostomies with benign and malignant disease.	Expert panel and patient focus groups	Focus Groups	None	None
Stoma-QoL	Prieto/ 2005 [288]	Development of an instrument to measure QoL in patients with an ileostomy or colostomy	4 Domains: Sleep, sexual activity, relations to family and close friends, and social relations to other than family and friends	4 point Likert Scale	20	Patients with a stoma	Patients with a stoma	Generated based on patient interviews	Semi-structured interviews	Assessed by a panel of lay people for linguistic clarity, understanding and ease of completion.	Cognitive interviews with stoma patients to assess for clarity.

Table 5-4 Psychometric and Operational Properties of Identified PROMS

Instrument	Validation Study Population	Convergent validity	Discriminant Validity	Internal consistency	Test-retest reliability	Known groups validity	Responsiveness to change	Non English language translations
City of Hope Quality of Life -Ostomy Questionnaire	Members of the United Ostomy Association for the state of California.	Pearson Correlation of each scale with single overall QoL item, r=0.24-0.76.	NR	Cronbachs α 0.95	NR	Significant association between new sexual concerns, social adjustment, general physical QoL, specific physical QoL, specific psychological QoL and gender.	NR	-
EORTC QLQ-C30	Non-resectable lung cancer	-	-	Cronbachs α 0.65-0.86	Pearson correlation coefficient: 0.82-0.92	Statistically significant differences between emotional functioning and pattern of malignant disease ($p<0.05$).	Statistically significant between group differences over time were observed for physical functioning ($p<0.001$), role functioning ($p<0.001$), fatigue ($p<0.01$), nausea and vomiting ($p<0.05$) and global quality of life ($p<0.01$).	

EORTC QLQ-CR29	Colorectal Cancer patients Stage I-IV (UK, France, Taiwan, Italy, Germany, Spain, USA)	-	Pearson correlation with the QLQ-C30 r<0.40	Cronbachs α 0.69-0.84	ICC >0.68 for all scales and >0.55 for single items.	Differences between known groups were observed in 16 of the 23 scales and items.	Statistically significant differences were observed over time for pain (p=0.045) and physical function (p=0.045)	
EORTC QLQ-CR38	Colorectal cancer Dutch patients Stage I-IV	-	-	Cronbachs α 0.38-0.91	ICC : 0.53-0.92	Effect size: 0.40-0.94	Statistically significant between group differences over time were observed in the expected direction (p=0.0001).	
FACT-C	Colorectal cancer patients Stage I-IV	Pearson Correlation of Colorectal Cancer Subscale with The Functional Living Index-Cancer 0.54 and with the Brief Profile of Mood States (BPOMS) - 0.46	Correlation of Colorectal Cancer Subscale with the Marlowe-Crowne Social Desirability Scale - 0.22	Cronbachs α 0.47-0.91	NR	Significant differences between three performance status ratings groups and the 5 subscales of FACT-c (p=0.0011)	Mean change in symptom improvement 5.59 (p<0.001).	Spanish

FACT-G	Breast, lung, colorectal, leukaemia/lymphoma, head and neck, prostate, ovarian, other primary cancers	Pearson Correlation with The Functional Living Index-Cancer 0.79	Pearson Correlation with the Marlowe-Crowne Social Desirability Scale - 0.22	NR	Pearson correlation coefficient: 0.82-0.92	Significant differences between stage of disease ($p<0.01$), performance status rating (<0.001) and location of questionnaire administration (p<. 0001)	Overall sensitivity to change demonstrated by all subscales $p<0.001$	-
MSKCC Bowel Function Instrument	Stage I-III Rectal cancer patients who had undergone sphincter preserving surgery	Pearson Correlation with EORTC QLQ 30: -0.53 - 0.36, with EORTC CRC-38 - 0.45 - 0.38 and FIQL 0.50 - 0.68	NR	NR	Pearson correlation coefficient: 0.62-0.87	Significant differences radiation treatment groups ($p=0.005$), type of surgery ($p=0.002$) and type of anastomosis (<0.0001).	NR	-
Stoma Quality of Life Scale (SQOLS)	70 consecutive ostomy patients (34 colostomy; 36 ileostomy)	Spearman's Correlation with SF-12 Physical Health and Mental Health Score 0.54-0.75	NR	Cronbachs α 0.72-0.89	ICC: 0.75-0.93	NR	NR	-
Stoma-QoL	182 patients from 4 European countries with stomas due to malignant and benign diseases			Cronbachs α 0.92	Spearman's Correlation coefficient >0.88	NR	NR	German, Spanish, French

Table 5-5 PROMS adherence to ISOQOL recommendations

ISOQOL Recommendations	***EORTC QLQ-C30***	***EORTC QLQ-CR38***	***EORTC QLQ-CR29***	***City of Hope Quality of Life-Ostomy Questionnaire***	**MSKCC Bowel Function Instrument**	**Stoma Quality of Life Scale (SQOLS)**	***FACT-C***	***FACT-G***	**Stoma-QoL**
Conceptual and measurement model	•	•	•	•	•	•	•	•	•
Reliability	•	•	•	•	•	•	•	•	•
Validity									
Content Validity		•	•	•	•	•	•	•	•
Construct Validity	•	•	•	•	•	•	•	•	•
Responsiveness	•	•	•				•	•	
Interpretability of Scores	•	•	•	•		•	•	•	•
Translation of PRO measure	•	•	•				•		•
Patient and Investigator Burden	•	•	•				•	•	•
% of ISOQOL recommendations covered	87.5	100	100	62.5	50	62.5	100	100	87.5

5.4.3 Domain and Subdomain Level Analysis

The nine identified measures covered between 16.6-50% of LRRC-specific domains and 5.5-38.8% of the LRRC-specific subdomains (Table 5.6). The LRRC-QoL domain of symptoms was covered by all the identified PROMS. None of the identified PROMs covered the domain of Healthcare Services. The subdomain of gastrointestinal symptoms was most commonly covered by the identified PROMS, with 77.7% of instruments covering this subdomain. The subdomains of disease management, treatment expectations and healthcare professionals were poorly covered. The FACT-G and FACT-C instruments covered the highest number of subdomains on the LRRC-specific conceptual framework, with each instrument covering 7 out of 18 subdomains.

Table 5-6 PROMS for Primary Rectal Cancer and LRRC-Specific Conceptual Framework: Content Analysis

LRRC specific subdomains	*EORTC QLQ-C30*	*EORTC QLQ-CR38*	*EORTC QLQ-CR29*	*City of Hope Quality of Life-Ostomy Questionnaire*	**MSKCC Bowel Function Instrument**	**Stoma Quality of Life Scale (SQOLS)**	*FACT-C*	*FACT-G*	**Stoma-QoL**
Symptoms	*	*	*		*	*	*	*	*
Pain and discomfort	•		•				•	•	
Gynaecological Symptoms									
Urological Symptoms		•	•						
Gastrointestinal Symptoms		•	•	•	•	•	•		•
Locomotor Symptoms									
Sexual Function		*	*			*			*
Sexual Intercourse		•	•			•			•
Healthcare Services									
Disease Management									
Treatment Expectation									
Healthcare Professionals								•	
Psychological Impact	*		*	*		*	*	*	
Mood	•		•	•			•	•	
Self-efficacy and dependence									
Appearance and Body Image			•			•			
Role Functioning	*			*		*	*	*	*
Work	•			•		•	•	•	
Social	•			•		•	•	•	•
Relationships	•						•	•	•
Future Perspective		*					*	*	
Disease Rerecurrence									
Further Treatments		•					•	•	
Future Plans									
Number (%) of LRRC-specific domains covered	3 (50%)	3 (50%)	3 (50%)	2 (33.3%)	1 (16.6%)	4 (66.6%)	4 (66.6%)	4 (66.6%)	3 (50%)
Number (%) of LRRC-specific subdomains covered	5 (27.7%)	4 (22.2%)	6 (33.3%)	4 (22.2%)	1 (5.5%)	5 (27.7%)	7 (38.8%)	7 (38.3%)	4 (22.2%)

5.5 Discussion

This review identified 9 PROMs that were developed and validated in primary rectal cancer for use in clinical practice and research. This review identified two core measures of HrQoL in cancer patients (FACT-G and EORTC QLQ-C30), three primary colorectal cancer specific measures (FACT-C, EORTC QLQ-CR38 and EORTC QLQ-CR29), three stoma specific measures (City of Hope Quality of Life-Ostomy Questionnaire, SQOLS and Stoma-QoL) and one disease specific, surgery specific measure (MSKCC Bowel Function Instrument). No disease specific measures were identified for LRRC.

Overall, there was a lack of overlap between the domains of the identified PROMs and the LRRC-QoL conceptual framework. The majority of the identified PROMs failed to encapsulate appropriate themes at domain and sub-domain level that are relevant to patients with LRRC. The FACT-G and FACT-C instruments covered the greatest number of LRRC-specific domains (66.6% each) and subdomains (38.8% each). Therefore, using existing PROMs, in their current format, to assess the HrQoL in LRRC is inappropriate as they do not provide a true reflection of the impact of LRRC, and thus lack content validity. There are a number of strategies which are available when existing PROMs fail to measure all relevant and identified domains [291] [281]. One strategy is to use multiple instruments to cover the relevant domains identified by the LRRC-QoL conceptual framework. The advantages of measuring PROs in this manner is the use of validated measures which lends credibility to the measurement strategy overall and allows for comparison between a number of studies. However, this was not a feasible option for measuring PROs in LRRC as combining domains from existing PROMs fails to capture all the domains identified by the LRRC-QoL conceptual framework, especially given that the domain of Healthcare Services was not covered by any of the identified measures. Furthermore, the use of different domains from a multitude of PROMs has a number of disadvantages include potentially increasing responder and administrative burden and cost. An alternative strategy to this is the modification of an

existing PROM [281]. Modifying the FACT-C questionnaire to reflect the needs of patients with LRRC is a possibility, as this instrument covered 66.6% of the LRRC-QoL. The FACT-C is a well constructed, psychometrically robust PROM, with a 100% adherence to the ISOQOL recommendations, which makes it a potential candidate for modification for use in the LRRC cohort. However, the FACT-C questionnaire would require significant modification to be able to appropriately measure PROs in patients with LRRC. This is evident by the fact that despite coverage of 66.6% of the domains of the LRRC-QoL, the FACT-C only covers 38.8% of the subdomains of the LRRC-QoL conceptual framework. The existing instrument would require significant revision of its current domains and the addition of two new domains to reflect the themes of sexual function and healthcare services. An alternative questionnaire which could be modified or combined is the EORTC QLQ-C30 and its colorectal modules CR29 and CR38. Although, these questionnaires only covered 50% of the LRRC-QoL domains and between 22.2 – 33.3% of subdomains individually, when these questionnaires are combined, they cover five out of the six (83.3%) LRRC-QoL domains and fourteen (77.7%) out of the eighteen subdomains. The LRRC-QoL domains which the EORTC questionnaires failed to cover adequately were the healthcare services domain and the future perspectives domain. Therefore, despite the good overall coverage, further work would be required to modify the EORTC questionnaires to enable future use in patients with LRRC.

Given the lack of overlap between existing measures and the LRRC-QoL conceptual framework, combined with the significant work required to revise existing PROMs to enable their use in LRRC, a pragmatic decision was made to develop a disease-specific PROM for LRRC. Using a combination of domains from a variety of instruments or modifying an existing PROM to measure PROs in LRRC to reflect the LRRC-QoL conceptual framework, although feasible options may not produce psychometrically robust and valid results in this complex cohort of patients without significant work. Given the degree of overlap between the EORTC questionnaires combined and the LRRC-QoL a pragmatic decision was made to

produce the LRRC-QoL, utilising guidance from the EORTC, including, using a similar design and identifying items from the EORTC item bank, with the end-user product made to be used as a supplementary module to the core EORTC QLQ-C30 module. Producing a disease-specific measure for use in LRRC would enable the measurement of HrQoL outcomes exclusively in this cohort of patients and allow for meaningful results to be obtained. Furthermore, disease specific measures are more sensitive in detecting changes due to the effects of the disease [170]. This would allow for detection of subtle differences between different subpopulation groups with LRRC when assessing treatment efficacy and impact, which would provide data in a more meaningful and clinically relevant manner.

5.6 Conclusion

This review has identified a number of PROMs for use in assessing outcomes in primary rectal cancer. The identified measures failed to adequately correlate with the LRRC-QoL conceptual framework. Consequently, these measures are inappropriate for use to assess PROs in LRRC. As no LRRC-specific PROM currently exists, a new PROM is required in this group of patients for use in clinical practice and future research.

6 Chapter 6 - Development and Pre-testing of the LRRC-QoL

6.1 Background

The process of designing and developing a new PROM is an exhaustive process, requiring a number of stages to be undertaken including 1) item generation, 2) pre-testing and 3) field testing to ensure a valid and psychometrically robust instrument is produced. The successful adoption of a newly developed instrument in clinical and academic practice is dependent on its content validity. Providing evidence for content validity demonstrates the link between the measurement concept and the score produced by the instrument in a specific context of measurement [89, 254, 292, 293]. Content validity is critical for determining how the results from future studies; including clinical trials and epidemiological studies, use the PROM to obtain meaningful clinical data.

The early developmental phases of a new PROM provides evidence for content validity by documenting that the proposed instrument represents the concept it intends to measure. Establishing content validity during the later stages of development focuses on instrument construction and respondent understanding, ensuring the methods employed to develop the instrument maintain the scientific rigour and credibility of the earlier phases [292]. During Phase II of the development, construction and pre-testing of the LRRC-QoL the emphasis on maintaining on-going content validity was on ensuring that the provisional instrument reached consensus regarding the format and instruction of the questionnaire, that the items were clear, unambiguous, understandable and relevant, with an appropriate recall period [259] , in a bid to develop an end product which was suitable for psychometric testing.

6.2 Design and Construction of LRRC-QoL

6.2.1 Item Generation

The aim of the first phase of item generation was to compile a comprehensive list of relevant issues specific to patients with LRRC. A systematic approach was employed to generate an exhaustive and unbiased item list, utilising three sources: 1) existing literature including existing instruments 2) patients and 3) clinical experts.

Existing literature

Two systematic literature searches were conducted identifying HrQoL issues relevant to patients with LRRC (Chapter 2) and patients undergoing exenterative surgery (Chapter 3). Patient cancer forums searches were conducted to supplement the item list generated from the literature review.

A further literature search was conducted identifying existing PROMs (Chapter 5). Items from these identified measures were mapped to the LRRC-specific conceptual framework to determine relevance to LRRC. Those considered relevant were included in the item pool.

Patient Focus Groups

Six focus groups were conducted; four in the UK and two in Australia, with a total of 23 patients participating to generate items (Chapter 4). All content was grouped into HrQoL domains, with each domain comprising a number of items describing different components.

Clinical Expert Panel

The clinical expert panel consisted of 6 surgeons, 2 clinical oncologists, 2 colorectal nurse specialists, a clinical psychologist and a public health epidemiologist, all of whom have a vast range of experience treating patients with LRRC and therefore have significant insight into patients experiences. The clinical expert panel reviewed the conceptual framework generated from the existing literature and patient focus groups and commented upon the clinical

relevance of the identified items and domains (Chapter 4). No new items or domains were generated following interviews with the expert panel.

6.2.2 Item Selection

Using the above three sources, a pooled list of HrQoL issues was generated. This list of HrQoL issues was converted into a list of questions utilising existing questions from the EORTC item bank [294]. Questions were sought from the EORTC item bank, which pools questions from all validated instruments previously developed by the organisation. Advantages of using existing questions include using questions which have previously undergone psychometric testing and have been proven to be useful, as well as saving time and effort.

In cases where the item bank yielded more than one item option for a particular issue all the potential options for this item were incorporated into the provisional list for expert clinical panel and patient review. In cases, where a suitable item option was unavailable the PROQUOLID database was consulted [295]. The PROQUOLID database is a comprehensive record of QoL and PROMs. If a suitable alternative was found in the PROQUOLID database the format of the item was adapted to achieve consistency with the EORTC format. In keeping with the FDA guidelines for developing new PRO instruments, questions were picked from the EORTC item bank and the PROQUOLID database which reflected the domains in question, related to the instruments objectives and used words which were familiar and non-confrontational, upsetting or ambiguous.

A total of 66 questions were mapped to the issues identified as a provisional item list (Appendix 4). This list of questions was administered to a group of clinical experts and

patients for review to ensure clarity, breadth of coverage and no overlap. A modified, online Delphi exercise was undertaken to determine item inclusion into the preliminary LRRC-QoL. An inclusion criteria of 75% agreement was set between all participants to include a question into the revised list. Multiple rounds of testing were conducted with removal of items which had reached the 75% level of agreement from subsequent rounds. A total of three rounds of testing were conducted. A total of 13 people participated in the modified Delphi, including 4 colorectal surgeons (2 British, 2 Australian), 2 clinical oncologists, 1 colorectal nurse specialist and 6 patients (4 male, 2 female; 3 British, 3 Australian). Consensus was achieved at the end of the third round with 43 items included and 23 items rejected. The revised item list consisting of the 43 questions is outlined in Appendix 5. Following this items were mapped onto the EORTC QLQ-C30 with any overlapping items removed from the LRRC-QoL. The final provisional item list consisted of 39 questions.

6.2.3 Construction of the LRRC-QoL

Design and Layout

The format of a questionnaire is central to its completion by its respondents [296-298]. A well designed questionnaire guides respondents through the instrument, motivating them to invest time and effort in ensuring completion [296]. Using existing guidelines careful consideration has been given to the design and format of the LRRC-QoL, including format and layout, scale construction, question ordering, response category format, time frame and administration [296, 298-301]. The general principles of questionnaire design dictate that a simple, clear and attractive format is employed, in keeping with these current recommendations [296, 302], the LRRC-QoL was designed as an A4 booklet, with size 12 Times New Roman font. A number of HrQoL questionnaires employ table grid lines to guide respondents through rows and columns, however, using the principles of cognitive design, these grid lines may represent barriers or stopping points and therefore may effect overall completion [296]. Consequently, it was decided to use dot leaders to guide responders horizontally across rows and upside

down triangles to guide respondents vertically. The LRRC-QoL design was broadly based on the design format of the EORTC questionnaires to ensure consistency between the core questionnaire (EORTC QLQ-C30) and our supplementary module. The use of a consistent design reduces the cognitive demands placed upon a respondent during questionnaire completion, enabling them to develop cognitive models for repetitive behaviours which are essential for navigating through the instrument and formulating responses [296, 298]. The main difference between the EORTC QLQ-C30 and the LRRC-QoL was the use of dot leaders and upside down triangles to guide responders horizontally and vertically.

The ability of respondents to comprehend instructions and questions appropriately is dependent on the presentation of the contextual information in an appropriate location. In the context of the LRRC-QoL, a decision was made to include a title page, introducing the general topic of the LRRC-QoL and thanking the respondents in advance for their participation. This has the advantage of gauging the respondents' interest and has implications on overall completion and data quality [298, 301, 303]. Instructions on completing the LRRC-QoL were placed at the start of the questionnaire and within the context of the questions to ensure retention of the instructions and ensure the questionnaire is completed appropriately [296].

Scale Construction

The process of scale construction or operationalisation is the grouping together of logically related items. Multi item scales break down complex variables into their component parts, thus improving validity, responsiveness and precision in measurement, however, this must be offset against the risk of responder burden [304-306]. The 39 items identified were operationalised into 5 scales of Symptoms, Psychological Impact, Sexual Function, Future Perspective and Healthcare Services to reflect the conceptual framework of the LRRC-QoL.

In constructing the scales for the LRRC-QoL a balanced view was adopted ensuring each construct was adequately operationalised with an adequate number of items to measure the construct in question, whilst maintaining an acceptable overall length of the LRRC-QoL. Section headers were used to help guide respondents through the scales/topics of the LRRC-QoL, this may help in completion of the overall questionnaire and potentially reduce responder bias [296].

Ordering of Questions

The ordering of questions can impact upon response bias [298, 304, 307]. Due consideration should be given to the ordering of items, with opening questions poised to be easy and non-threatening. Opening questions should be relevant to respondents' circumstances, thus highlighting the relevance and importance of the questionnaire and encouraging completion. Controversial, emotive and sensitive questions should be avoided early on in the questionnaire to encourage completion [298, 307]. Based on the qualitative work carried out in patients with LRRC a combination of symptoms were common to all patients, therefore the decision was made to open the LRRC-QoL with questions regarding symptoms. Sensitive items regarding sexual function, body image and psychological well-being were embedded in the middle of the questionnaire.

A number of questions may not be relevant or applicable to all patients with LRRC, in these instances skip questions have been introduced within the format of the LRRC-QoL to guide respondents to the next appropriate question and to reduce overall responder burden.

Response Category Format

The response category format is largely dependent on the nature of the underlying question. A number of different scales exist, including frequency scales, Thurstone scales or Likert scales [304]. Frequency scales establish how often a target behaviour or event has occurred [307].

Thurstone scales use empirical data derived from judges to measure attitudes along a continuum [304, 307]. Likert scales use fixed choice response formats, measuring attitudes and opinions on a linear scale. Likert scales are the commonest rating scales to be used in PROMs and therefore this was the method of choice for LRRC-QoL. This decision was partially influenced by the use of items from EORTC item bank as the response category format for these questions was a 4 point Likert scale. It was therefore decided to maintain this response format to maintain consistency with the core EORTC questionnaire.

Time Frame

An appropriate recall period must be selected to ensure that appropriate changes due to disease burden or impact are captured, whilst minimising the potential of response bias. Setting too long a time period may lead to the under reporting of events occurring, whilst a shorter time frame may not be appropriate as clinically relevant events may not yet have occurred. Furthermore, a standard, universal time frame may not be appropriate for all the scales being measured. With regards to the LRRC-QoL, it was decided two time frames would be used, a shorter time frame of 1 week to assess symptoms, psychological impact and role functioning and a longer time frame to assess sexual function, future perspective and healthcare services. This was based on clinical grounds, as changes in LRRC symptomology and severity can change over the course of a week and therefore a longer recall period would risk not capturing relevant changes to HrQoL, whereas sexual function, future perspective and healthcare services impact will have a prolonged impact and therefore will remain static over a longer period of time.

Expert Appraisal

Prior to the commencement of the pre-testing of the LRRC-QoL an expert panel comprised of 5 colorectal surgeons (2 British, 3 Australian), 2 clinical oncologists and 3 colorectal nurse specialists reviewed the preliminary version with an emphasis on question wording, ordering,

format and relevance. Amendments were made to the LRRC-QoL format and ordering of questions which led to the production of a preliminary LRRC-QoL ready for pre-testing (Appendix 6).

6.3 Pre-testing of the LRRC-QoL

The pre-testing of a PROM is essential in establishing content validity to ensure responders in the target population find the questionnaire to be relevant, appropriate, comprehensible and understandable prior to final field testing [89, 254, 292, 293].

The principles of Cognitive Aspects of Survey Methodology (CASM) have been widely used in pre-testing questionnaires to investigate and understand the cognitive processes employed by respondents in reading, comprehending and interpreting questions and in formulating a response to a set questions [308, 309]. Cognitive interviewing aims to reduce measurement error in questionnaire design, with particular emphasis on response error. Underpinning this, is the four stage model proposed by Tourangeau, which consists of the cognitive processes of comprehension, retrieval, judgement and response whilst formulating a response to questionnaire items [310]. The four stages highlighted by this model are applicable in the context of assessing HrQoL as responders are expected to understand complex questions, deal with abstract concepts, effectively retrieve information from long term memory, aggregate that information, apply frequency judgements, magnitude estimations and decision heuristics in selecting which response category to endorse [309, 311].

6.4 Aims and Objectives

The aims of this study were:

- To assess respondent comprehension of LRRC-QoL. This included evaluation of the wording and format of the questionnaire, instructions, item stems, recall period and response options.

- To evaluate the comprehensiveness and relevance of the LRRC-QoL to its target population.
- To ensure the cross-cultural equivalence of the LRRC-QoL between British and Australian participants.

6.5 Methods

6.5.1 Cognitive Interviews

Face-to-face cognitive interviews were undertaken to investigate the cognitive processes involved whilst completing the preliminary version of the LRRC-QoL (Appendix 6) in both population groups. The principles from Tourangeau four stage cognitive model were used to identify, understand and evaluate patients responses to the LRRC-QoL.

There are two main types of cognitive interview; concurrent and retrospective [312]. Concurrent interviewing involves the respondent providing a verbal account of their thinking as they work through the questionnaire. Retrospective interviewing involves questioning the respondent upon completion of the questionnaire. In this study both methods were employed, with concurrent interviewing used to assess responder understanding with regards to item content, wording and format. Retrospective interviewing was used to evaluate questionnaire design with emphasis on overall format, completion time, recall period and response options.

The interview techniques of ‘think-aloud’ and ‘verbal-probing’ were both incorporated when undertaking cognitive interviews. The think-aloud technique enables respondents to verbalise thoughts during the completion of the questionnaire, this is interpreted as a representation of the respondents memory, language, comprehension and problem-solving processes [312, 313]. Verbal probing involves asking respondents to paraphrase questions, to clarify the definitions of wording within questions, explain the rationale behind responses and identify areas of the questionnaire that pose difficulty in understanding, interpretation or completion [312]. The key differences between the two interview techniques are highlighted below [314]:

Think Aloud	Verbal Probing
Respondent driven	Interviewer driven
Lower interviewer burden	Lower respondent burden
Potential for difficulty to be experienced by the respondent during the interview	Easier interview for the respondent

Cognitive Interviews Methodology

Face-to-face cognitive interviews were undertaken to assess the processes of comprehension and response formulation during questionnaire completion. Participants completed the preliminary LRRC-QoL without assistance. Both interview techniques, of think-aloud and verbal probing, were employed during the interview. A standardised semi-structured cognitive interview guide informed all cognitive interviews (Appendix 7). Participants were guided through each item whilst encouraged to engage in the think-aloud process followed by verbal probing with questioning using prescribed interview scripts and standardised probes. The use of scripted questions and probes ensured standardisation across all interviews and ensured overall consistency and objectivity. Scripted probes were developed ensuring there was no bias in phrasing of words. All probes were developed based on the four stage Tourangeau cognitive model (Table 6.1). All interviews were recorded and transcribed verbatim.

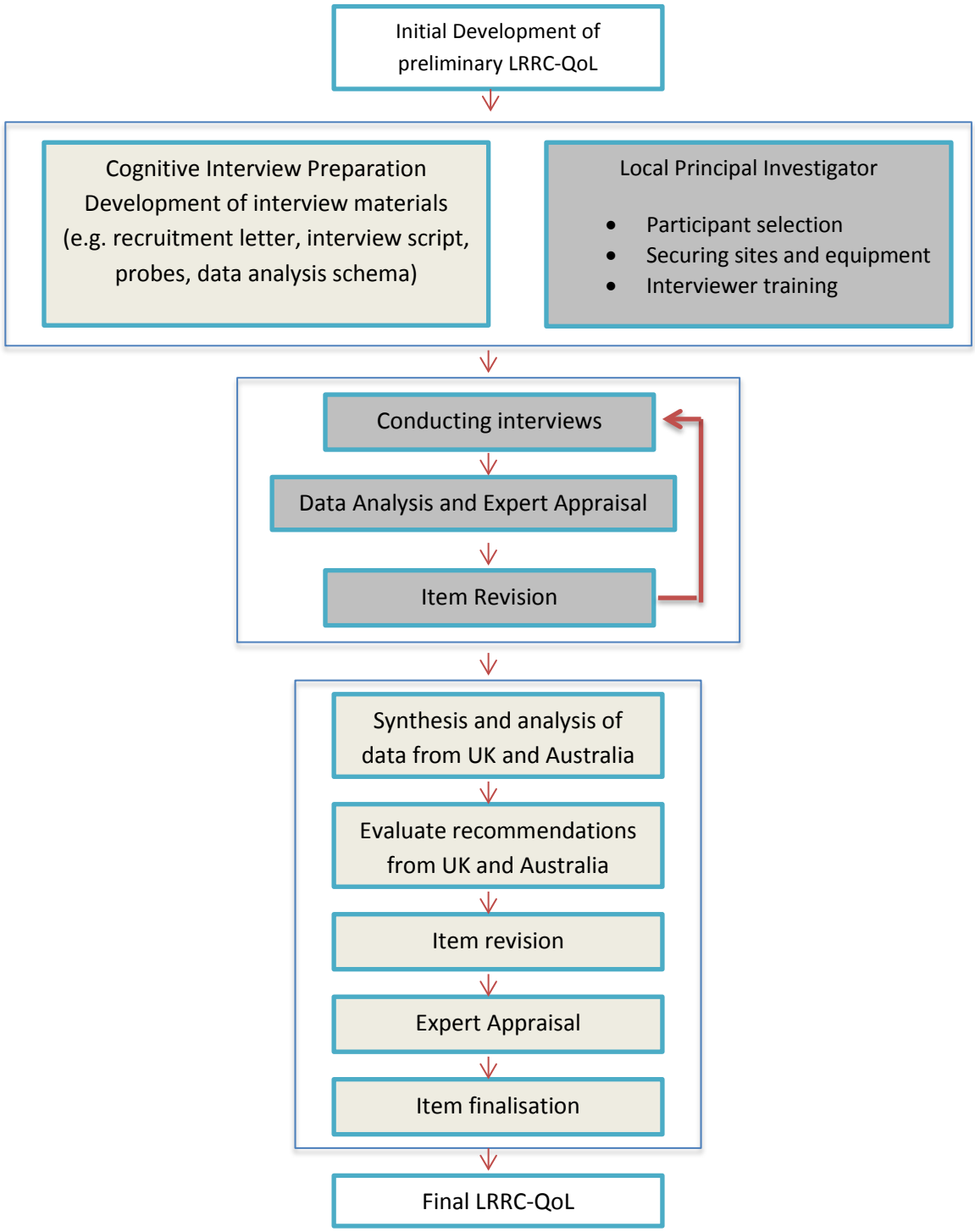
Table 6-1 Examples of Cognitive Probes

Cognitive Component	Definition of Cognitive Probe	Interview Probe
Comprehension	Respondents' interpretation of a question by determining what they believe the question is asking based on the meanings of specific words and	What does the word x mean to you? What do you understand by x?

	phrases.	
Retrieval	Relevant information retrieved from long-term memory to enable a response. Explores the strategies used to retrieve the relevant information.	How did you remember that? Did you have a particular time period in mind?
Judgement	Retrieved information evaluated for its relevance to the question and is judged for its completeness	How did you arrive at that answer? How well do you remember this?
Response	Initial response is considered for acceptability and consistency, which is mapped onto a response category.	How did you feel answering this question? Were you able to find your first answer to the question from the response options shown?

Due to the international nature of this study cognitive interviews and data analysis were undertaken individually within the two countries, this was done to ensure a multinational perspective was incorporated into the pretesting of the LRRC-QoL. The analyses from the two countries were synthesised and the recommendations from both countries were evaluated, with appropriate revisions made and analysed by the expert groups in both countries prior to finalisation of the LRRC-QoL. An overview of the data analysis plan is outlined in Figure 6.1.

Figure 6-6-1 Overview of Data Analysis Plan



6.5.2 Data Analysis

Data analysis was conducted in the same manner in both the UK and Australia, with review and analysis of all data from individual cognitive interviews conducted after a minimum of 3 interviews, with subsequent review of any revisions to the LRRC-QoL by the expert panel

prior to further testing. This method of multiple rounds of pretesting enabled problems to be identified and rectified at an early stage and ensured no new problems had been introduced secondary to the revisions. This iterative process was continued up to the point of saturation in both population groups.

The LRRC-QoL was analysed in a systematic manner using the Question Appraisal System (QAS-99) [315]. The QAS-99 is a coding tool, which categorises item problems identified during the cognitive interview process. It consists of eight major categories, which includes reading, instructions, clarity, assumptions, knowledge, sensitivity/bias, response and other problems. These categories focus on question characteristics that are likely to present problems when completing and forming responses to questionnaires.

Expert Panel Analysis

Following each round of cognitive testing, the expert panel reviewed all findings within and across the interviews. Each item was individually considered when deciding whether to retain, revise, eliminate or add further items to the LRRC-QoL. Decisions made to make revisions to the design and format of the LRRC-QoL were made by consensus. These decisions were made based on similar comments made by a number of participants or a single comment, if this was deemed sufficiently important. The clinical relevance of the LRRC-QoL was assessed with each revision and round of cognitive interviews.

6.6 Results

6.6.1 Patient Demographics

A total of 27 patients participated in this study between November 2013 and June 2014, with 16 participants from the UK and 11 from Australia, with a median age of 62. Patient demographics, clinical and operative data are outlined in Table 6.2. Median time elapsed

between diagnosis or treatment of LRRC and interview date was 12 months (IQR 5-16). Patients were selected to ensure representation of disease subsite, the presence of concurrent metastatic disease and the use of multimodal preoperative treatments.

Table 6-2 Patient and Clinical Demographics

Factor	*Number of Patients*
Median Age	62 (IQR 42 - 83)
Gender	
Male	18
Female	9
Primary Operation Type	
Anterior Resection	17
Abdominoperineal Excision of Rectum	4
Hartmaans Procedure	4
Proctocolectomy	2
Neoadjuvant Treatment – Primary Cancer	
None	16
Chemoradiation	8
Radiotherapy	3
Adjuvant Treatment – Primary Cancer	
None	15
Chemotherapy	9
Chemoradiation	1
Radiotherapy	2
Reason for Detection of Recurrence	
Surveillance	14

Symptoms	13
Neoadjuvant Treatment – Recurrent Cancer	
None	12
Chemoradiation	12
Chemotherapy	4
Adjuvant Treatment – Recurrent Cancer	
None	24
Chemotherapy	3
Subsite Location	
Central	10
Anterior	5
Posterior	7
Lateral	5
Operative Procedure for LRRC	
Total Pelvic Exenteration	8
Anterior Pelvic Exenteration	4
Posterior Pelvic Exenteration	4
Excision of recurrent tumour mass	3
Completion proctectomy	5
Composite abdominosacral resection	3
Current Disease Status	
Disease Free	18
Local Disease Re-recurrence	4
Distant Metastatic Disease	2
Local and Distant Disease	3

6.6.2 Cognitive Interview

Median length of the interview was 85 minutes (IQR 40 – 100). In both the UK and Australian groups saturation was reached following the third round of pretesting. Cognitive interviews identified issues with the content of LRRC-QoL in both study populations.

6.6.2.1 British Cohort

The QAS-99 system was used to categorise all identified issues throughout all cognitive interviews (Table 6.3). In the British cohort a total of 16 items were identified as problematic using the QAS-99 tool. This led to the removal of 4 items, the merging of 7 items, the revision of 1 item and an addition of an extra item. The LRRC-QoL underwent revision on two occasions with the final version (British) in this cohort of patients consisting of 31 items (Appendix 8 and 9, Figure 2). The QAS-99 identified issues within the categories of clarity, assumptions and other problems in this cohort. Within the category of clarity, a total of 6 items were identified. Ambiguities arose within this category when trying to understand the meaning of the word 'perception' in Question 20 'Do you think others perception of you has changed following your medical diagnosis and treatment?' with all participants in the first round of cognitive testing requiring clarification of the meaning of 'perception' and deeming the question vague and irrelevant following explanation. Further areas of contention included items referring to future health perspectives, with participants stating Question 31 'Have you been worried about your health in the future?' and Question 32 "Have you felt uncertain about the future?' were sufficiently similar, with the former question being grammatically ambiguous as it referred to the past tense when asking about the future, as well as, pre-empting the answer to the next question. The wording of question 32 was preferred and therefore this was retained. Similar observations were made regarding the items referring to patient satisfaction with healthcare professionals and services, with Questions 33 'Were you satisfied with the information the healthcare professionals gave you about your illness?', Question 34 'Were you satisfied with the information the healthcare professionals gave you about your treatment?' and Question 35 'Are you satisfied with the diagnosis, treatment and

medical follow up provided?'. The format and wording of Questions 33 and 34 were preferred and therefore these two questions were merged and Question 35 removed.

Within the assumptions category, Question 36 'Are you satisfied with the length of your recovery?' was categorised as assuming a constant behaviour by all participants in the first round of pre-testing. Participants felt that it was assumed that recovery occurred within a pre-defined period of time, whereas in actual fact recovery was viewed as a continuum, which is difficult to measure quantitatively, with pre-morbid functional capacity not being truly achieved and a number of adaptations being made to accommodate post-operative functional status.

Other identified issues related to the content, with participants stating there was no item focussing on wound related issues including pain and discharge, as a result the question 'Have you had any pain or discharge from your wound?' was added to the questionnaire. However, pre-testing in the second round of cognitive interviews revealed participants interpreted the word 'wound' as an open, healing surgical incision which would describe the initial post-operative phase and preferred the addition of the word 'scar' to denote the incision during the latter phases. Question 10 'Are you worried about your mobility' which was part of the subscale symptoms was deemed to be out of keeping with the other questions in this subscale. Participants felt this question referred to the psychological component of the impact of reduced mobility on overall HrQoL and not its physical impact as per the other questions in this subscale. Furthermore, participants did not attribute issues related to mobility to their diagnosis or treatment of LRRC, consequently this question was removed.

Figure 6-2 Flow diagram demonstrating modifications and retentions using the Symptoms Subscale in the UK Cohort as an example

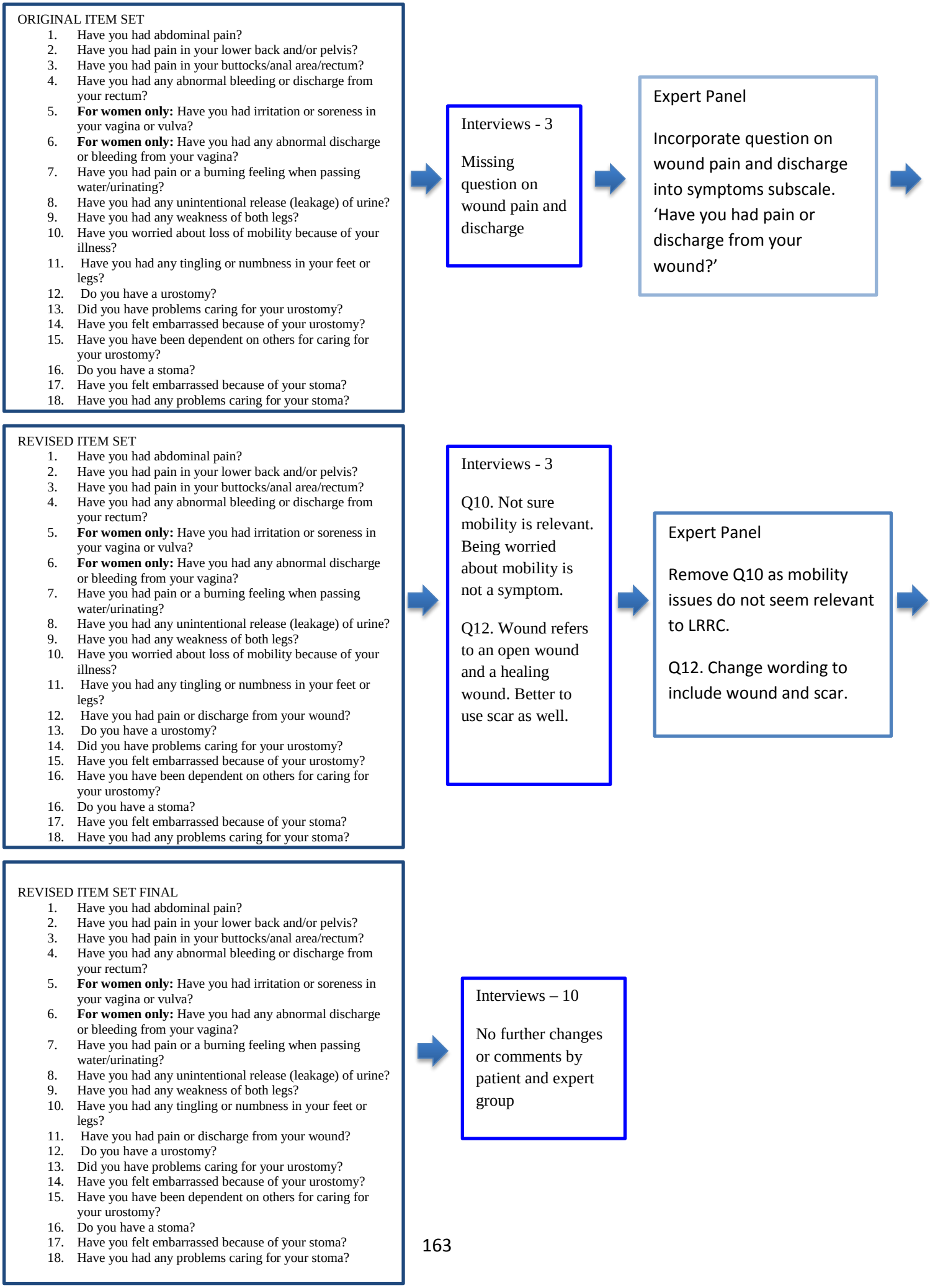


Table 6-3 Identification of Issues with LRRC-QoL using the QAS-99 System

QAS-99 Coding Category	Number of Items UK Cohort	Number of Items Australian Cohort
Reading		
What to read	0	0
Missing Information	0	0
How to read	0	0
Instructions		
Conflicting or Inaccurate Instructions	0	0
Complicated Instructions	0	0
Clarity		
Wording	5	5
Technical Terms	0	1
Vague	1	1
Reference Periods	0	0
Assumptions		
Inappropriate assumptions	0	1
Assumes constant behaviour	1	0
Double –Barrelled	0	0
Knowledge		
Knowledge	0	0
Attitude	0	0
Recall	0	0
Computation	0	0
Sensitivity/Bias		
Sensitive Content	0	0
Sensitive Wording	0	0

Socially Acceptable	0	0
Response		
Open-Ended	0	0
Mismatch	0	0
Technical Terms	0	0
Vague	0	0
Overlapping	0	0
Missing	0	0
Illogical Order	0	0
Other Problems		
Recurring/Similar Question	7	6
Missing Question/Content	1	2
Irrelevant Question	1	0
TOTAL No OF IDENTIFIED ITEMS	16	16

6.6.2.2 Australian Cohort

In the Australian cohort the QAS-99 system identified 16 items as problematic, which led to the revision of 8 items, the merging of 5 questions, the removal of 5 items and the addition of an extra item (Table 6.3). Problems were identified within the categories of clarity, assumptions and other problems. The LRRC-QoL underwent revision on two occasions with the final version (Australian) in this cohort of patients consisting of 32 items (Appendix 10 and 11).

A number of items were revised to improve clarity, relevance and patient comprehension, this included Question 9, which was revised from ‘weakness in both legs’ to ‘either or both legs’ to reflect patients with unilateral symptoms. Question 10 ‘Are you worried about your mobility’ was revised with substitution of the ‘worried’ with ‘difficulty’ as patients felt it was the physical act of walking which was impacted upon and this was more in keeping with the rest of the questions within the symptoms subscale. Question 12 ‘Do you have a urostomy?’ was revised to include the word ‘urine

bag' as this was the colloquial term used and better understood by patients. Similar issues were identified with Question 20 regarding perception of others as the British cohort with misinterpretation of the meaning of the word 'perception'.

Question 23. 'Have you felt less interest in sex?' was revised to 'Have you felt interest in sex?' as the former question suggested a baseline interest in sex which may not be applicable to all patients. Similarly, Questions 24 and 25 regarding difficulty gaining or maintaining an erection and ejaculation problems were rephrased from 'Did you have difficulty gaining or maintaining an erection?' to 'How difficult is for you to gain/maintain an erection?' and from 'Did you have ejaculation problems (e.g. dry ejaculation)?' to 'Have you had ejaculation problems?'. Patients felt the use of the word 'did' referred to the past tense and did not reflect their current sexual status and therefore found the question confusing.

Within the assumptions category Question 36 'Are you satisfied with your length of recovery?' was removed as participants felt this question was not applicable in the pre-operative phase and therefore could be potentially confusing.

Patients felt there was repetition in asking questions about future health status and satisfaction with healthcare professionals and services with Questions 31-32 and Questions 33-35, therefore these questions were amalgamated into two individual questions.

Inclusions to questions were made to reflect the full spectrum of HrQoL issues related to patients with LRRC, this includes Question 4 which was revised to include faecal leakage as part of the complement of rectal symptoms. Question 37 'Were you satisfied with the knowledge and experience of your doctors?' was revised to 'your specialist team including doctors/nurses/specialist nurses' as this reflected the multidisciplinary management of LRRC, thus enabling patients to comment on their complete experience. One new question was included regarding wound related issues including pain and discharge.

6.6.2.3 Questionnaire Format

The self-complete mode of administration was acceptable to all patients, with all patients stating the instructions were clear, concise and easy to understand. The overall format of the questionnaire was acceptable to patients with easy to understand and follow response options. Patients commented on the different recall periods of 1 week and 4 weeks for the short-term issues of symptoms and psychological impact and sexual function, future perspective and healthcare services respectively, stating the recall period could be better highlighted. Consequently, the format of the recall period was changed to highlight the differences by using italics and underlining.

6.6.2.4 Comparative Analysis

On review of the final LRRC-QoL questionnaires from both population cohorts (Appendix 9 and 11), similar issues with the questionnaire were highlighted, such as, difficulties with understanding the word 'perception', repetition of questions on future health and satisfaction with healthcare services, irrelevance of the length of recovery and the inclusion of an item on wound related pain and discharge. Two items and one skip question were removed from both population groups due to overlap with the EORTC QLQ-C30 core module and one skip question was removed regarding sexual activity due to the loss of potentially important data. The main differences between the two final versions were the retention and revision of the question regarding mobility by the Australian cohort. There was consistency within the wording of the majority of items with differences observed in 7 items alone. The inconsistencies were solved by consensus through discussion by the expert panel to produce a final overall version of the preliminary LRRC-QoL (Appendix 12, Table 6.4).

Table 6-4 Comparative Analysis of British and Australian versions of the LRRC-QoL

British Version	Australian Version	Expert Panel Analysis
Have you had any abnormal bleeding or discharge from your rectum?	Have you had any abnormal bleeding, discharge or faecal leakage from your rectum?	Include faecal leakage into question.
Have you had any weakness of both legs?	Have you had any weakness of either or both legs?	Accept Australian version as accounts for unilateral and bilateral symptoms.
Question removed	Have you had any difficulty in walking?	Include question – highlighted in Phase I of focus groups. Relevant to patients with high sacral resection and sciatic nerve involvement.
Do you have a urostomy?	Do you have a urostomy (urine bag)?	Include urine bag as improves patient comprehension of the question.
Have you felt less interest in sex?	Have you felt interest in sex?	Remove 'less' as suggests baseline level of interest.
Did you have difficulty gaining or maintaining an erection?	How difficult is it for you to gain or maintain an erection?	Accept Australian version as assesses current status.
Did you have ejaculation problems (e.g. dry ejaculation)	Have you had ejaculation problems (e.g. dry ejaculation)?	Accept Australian version.
'Were you satisfied with the knowledge and experience of your doctors?	Were you satisfied with the knowledge and experience of your specialist team (Doctors/ Nurses/Specialist Nurses/ Physiotherapists)?	Accept Australian version

6.6.3 The Final LRRC-QoL

The final LRRC-QoL consists of 32 questions organised into 5 scales; Symptoms, Sexual Function, Psychological Impact, Future Perspective and Healthcare Services (Appendix 12). This final version was used in the final field study to document the psychometric properties of the LRRC-QoL.

6.7 Discussion

This study uses a multinational approach in establishing the content validity of the LRRC-QoL by conducting cognitive interviews in both the UK and Australia prior to final psychometric validation. This enabled a truly multinational perspective to be gauged, identifying and rectifying issues specific to both population groups, thus minimising the potential for responder error across both population groups. This was a cross-national study incorporating two countries with a number of common social and political perspectives and a common language. In such studies, it is the cultural variance in HrQoL conceptualisation, validation and expression that is important [316].

Ensuring cross-cultural equivalence is a prerequisite for conducting cross-national HrQoL research [317]. This encompasses four areas which include conceptual equivalence, operational equivalence, item equivalence and scalar equivalence [318]. Conceptual equivalence refers to the overlap in construct conceptualisation across different groups thus ensuring concepts hold similar meanings in all groups, this was demonstrated through Phase I of the development of the LRRC-QoL. Operational equivalence ensures no bias is introduced through the mode of administration of the questionnaire, item and response format [317]. This was demonstrated in this study with patients from both population groups stating the questionnaire format was acceptable, understandable and easy to follow. Item equivalence ensures items measure the same concepts in different cultures and nations, this has been demonstrated within this study. Finally, scalar equivalence is achieved when a construct is measured on the same metric, this will be tested in the final phase of development of the LRRC-QoL.

Item equivalence between the British and Australian populations was assessed using the QAS-99 coding system. The commonalities between the two populations were manifested in this study by the similarity of issues raised when assessing the LRRC-QoL, thus demonstrating item equivalence. The issues identified by the QAS-99 were multifactorial, identifying three key areas of potential for responder error, these included the categories of clarity, assumptions and recurring questions. The majority of the issues related to the clarity of the questionnaire, with difficulties identified within the subcategories of wording, technical terms and vagueness. Problems relating to the clarity of a question are often associated with the respondents meaning and use of words and the context in which they are used in the questionnaire. Words that are familiar to one group may not be to another or they may have a different meaning [312]. This is illustrated in the pretesting of the LRRC-QoL, as the British cohort of patients understood the meaning of the technical term urostomy, whereas the Australian cohort were not familiar with this technical term and preferred the use of the colloquial term, urine bag. This issue arose due to an overestimation of the understanding of medical terminology by the target population [312]. To ensure the cross-cultural equivalence both terms were retained within the final version of the LRRC-QoL. The other main issue identified in both population groups was the number of recurring questions on similar themes, which required amalgamation to streamline the questionnaire, reduce respondent burden and improve patient comprehension. Other issues related to the assumption category with the item in question assuming that recovery is a constant and not a dynamic continuum which begins in the post-operative phase and therefore will not be applicable in the pre-operative phase. The presence of this question led to considerable confusion amongst participants as it was unclear whether the question referred to the recovery from the initial surgery for the primary rectal cancer or the recovery from the second recurrent rectal cancer surgery.

The use of a coding system enabled a transparent and robust method of identifying and correcting arising issues within the framework of the LRRC-QoL questionnaire to ensure item equivalence

between the two population groups. The use of the QAS-99 coding system ensured data was interpreted in a structured and systematic manner thus reducing the potential for measurement error in both cohorts and enhancing the overall validity of the data acquired [312]. Furthermore, the QAS-99 provided an efficient and effective manner of dealing with a relatively large volume of data [319, 320]. The limitations of a coding system include identifying issues that lie outwith the predefined categories of the system, to circumvent this limitation it is essential to select a flexible system which enables all identified categories to be recognised. The advantage of using the QAS-99 system is that it offers flexibility within its structure through the incorporation of the 'other' category, this enables the researcher to identify and categorise issues that do not fall within the structure of the coding system.

When conducting cross-national research a number of procedural and pragmatic issues must be consider. Procedural issues relate to target country teams, data analysis, translation, data documentation and evaluative criteria [317]. Procedural issues were not encountered in this study due to the involvement of two countries alone, both with the common language of English, with teams that had worked together in Phase I of the development of the LRRC-QoL. To minimise issues of data analysis, data documentation and evaluative criteria, a study format (Figure 6.1) was decided by teams within both countries prior to study commencement. Data analysis was undertaken at a local level in both countries by the same researcher (DH) to minimise interpreter bias. The British interviews and analysis was conducted first. Upon completion of the Australian analysis, a second round of analysis was undertaken across both population cohorts to minimise bias and ensure all appropriate issues were highlighted and captured. To ensure objectivity in data documentation and evaluative criteria a standardised topic guide, data collection sheets and systems (QAS-99) were employed. Pragmatic issues relate to the interviewers skills and experience, respondents characteristics, topic sensitivity and communication style, which can arise due to potential variations between participating countries [317]. To overcome the issue of variations amongst interviewers standardised probes and scripts were employed during the interview process. Furthermore, the British researcher (DH) conducted and oversaw interviews in Australia as well as in the UK to ensure

standardisation across all cognitive interviews. Respondent characteristics are important for extracting pertinent data from the participants. To encourage an open and comfortable environment local interviewers led or oversaw all cognitive interviews, with appropriate modification of interview probes as necessary. Topic sensitivity was determined during Phase I of the development of the LRRC-QoL which involved both British and Australian patients, this in turn informed this study, subsequently no issues with topic sensitivity were encountered in this study. Besides the logistic difficulties of conducting interviews and analysing data in two different countries no other procedural or pragmatic issues were encountered in this study, this is primarily due to the commonality of the English language and the similarities in cultural and social norms between the two population cohorts.

Despite the issues involved in conducting cross-national research and the logistical difficulties of conducting studies sequentially in Britain and Australia, it was deemed appropriate to include the Australian cohort within this project. The Australian team have a longstanding interest in researching QoL in patients with advanced pelvic malignancy, including LRRC [191, 321, 322] and expressed an interest in developing a LRRC specific PROM. In addition to this, the Australian team has a leading, international reputation in performing ultra-radical surgery in this cohort of patients with good clinical outcomes [22, 24]. By including the Australian cohort ensures the opinions, thoughts and experiences of patients with advanced disease requiring an ultra-radical resection are appropriately captured. This will ensure the LRRC-QoL is applicable to all patients with LRRC.

Cognitive interviews are a commonly used method of pretesting HrQoL instruments. There are a number of cognitive interview techniques available; this study employed the think-aloud and verbal probing techniques. Think aloud techniques encourage respondents to verbalise their thoughts during questionnaire completion, thus enabling an insight into the respondents' memory, comprehension and problem-solving strategies. The limitations to this method of cognitive interviewing include difficulty to articulate thought processes by some respondents during questionnaire completion, with thought processes being affected by this technique thus leading to an assumption that problems may exist within the questionnaire when they do not. The combination of the think aloud technique with verbal probing can help overcome some of these limitations. However, cognitive interviews have a number

of common limitations irrespective of technique. Cognitive interviews are often criticised for the artificial environment in which they are conducted and the 'cognitive load' they confer on respondents using techniques such as think-aloud and verbal probing when completing a questionnaire. The presence of a researcher contributes further to the artificiality of the situation and may introduce bias into the cognitive process. A further limitation of cognitive methods is the reliance on respondents' verbal responses, when not all cognitive processes can be verbalised (e.g. gender). The overarching limitation of cognitive interviews is that they are qualitative in nature and therefore they can only identify problems, they cannot provide information with regards to the extent or the size of the impact on survey estimates [314]. Cognitive methods enable the pre-testing of existing questions and enable the testing of proposed revisions to the original question, however, they cannot provide quantitative evidence on whether proposed revisions are better than the original question [314]. To supplement the qualitative methodology there are new emerging quantitative methods such as Rasch analysis and Item-response theory which can assess how well items address the entire continuum of patient experience of the concept, thus potentially corroborating and expanding with qualitative data. However, these quantitative methods should not be used in isolation but in combination with recognised qualitative methodology, as in the absence of prior knowledge, frameworks and qualitative data, a theoretical instrument can be developed producing scores with unknown meaning.

6.8 Conclusions

This study documents the content validity of the LRRC-QoL as it is extended from a conceptual framework to a preliminary version ready for psychometric testing. It reports the process of instrument and item crafting, achieving consensus on format and structure and documents respondent understanding and acceptability through structured cognitive interviews, thus providing on-going evidence for the LRRC-QoL's content validity.

7 Chapter 7 – Psychometric Evaluation of the LRRC-QoL – Methodology and Recruitment

7.1 Background

For any PROM to be applied in clinical practice and research its scientific validity, rigour and credibility must be established prior to its use. The development of PROM is a complex methodological process, consisting of a number of key steps which help ensure its overall robustness, validity and credibility. This process must be transparent and accurately documented. To ensure a PROM is developed in a systematic fashion a number of regulatory authorities have produced a series of guidelines which outline the process of PROM development [212, 274, 283, 323]. Thus far, the LRRC-QoL has been developed in accordance with these guidelines by establishing the content validity of the LRRC-QoL in Phase I (Chapter 2-4), development of a conceptual framework (Chapter 4) and pre-testing and refinement of the provisional questionnaire in Phase II (Chapter 6). The final phase of developing any PROM prior to its wider dissemination in academic and clinical practice involves assessing and measuring its psychometric properties using quantitative measures. Key properties of a PROM are measured including reliability and validity during the final field testing. Reliability refers to the extent to which the PROM is free from random error, whereas validity assesses whether the instrument measures what it purports to measure. These are required prerequisites for psychometrically validating a PROM as it gives meaning to the results and scores obtained from the instrument.

7.2 Classical Test Theory

Classical Test Theory (CTT) is a traditional quantitative psychometric approach employed to test the reliability and validity of a scale based on its items. CTT consists of a number of key principles and

statistical tests for developing and assessing measures including PROMS to determine how successful they are at estimating unobservable variables of interest such as HrQoL.

Underpinning CTT is the assumption that each observed score (X) on a PROM is a combination of the underlying true score (T) and random error (E).

$$X = T + E$$

CTT assumes that each person has a true score (T), which can be observed if there are no errors in measurement. A person's true score is defined as the expected score over an infinite number of repeat measurements of the scale, as this is not practical T is essentially a hypothetical measure. Therefore, CTT assumes the average of the observed score ($\bar{x}$) is the best estimate of the true score. The second assumption of CTT is that the random error (E) found is normally distributed and therefore the expected value of theses fluctuations (i.e. mean of the distribution of errors over a hypothetical infinite number of administrations for the same subject) is taken to be 0. Furthermore, random errors are assumed to be uncorrelated with a true score, with no systematic relationship between a true score and whether a person has positive or negative errors.

Reliability

CTT enables the reliability of an individual item (i.e. the magnitude of error) to be calculated. A good item should yield a score that is a close and accurate reflection of the true score. The assumption that the true score varies across and within individuals during repeated measurements suggests the observed score should also mirror this variation. The equation for this process is:

$$VAR(X) = VAR(T) + VAR(E)$$

The proportion of variance between the true and observed scores should provide information regarding how well the item in question serves as a proxy for the true score i.e. the proportion of the

item's variation that was shared with the true score. This is defined as the item's reliability (R).

$$VAR(T)/VAR(E) = R$$

When the variance of the true score is high relative to the variance of the observed score the reliability (R) will be high. Conversely, if the variance of the true score is low relative to the variance of the observed score the reliability will be low. Reliability values usually range from 0.00 – 1.00, thus rearranging the above equation to:

$$R = 1 - (VAR(E)/VAR(X))$$

Reliability is equal to 1 – the ratio of random error variance to total score variance.

The items within a scale must be unidimensional i.e. they must be indicative of the same underlying variable and thus associated with the true score of that variable. The error associated with each item must be independent of the true score and of the errors arising from the other items within the scale. Each item within the scale must be a good indicator of the true score i.e. item covariances with true score must be equal across the items and the magnitude of the respective error contributions to the total variance of each item must be equal across items. According to these criteria, the correlation between any two items is equal to the product of correlation of each item with the true score. The correlation between two items, A and B (Rab) will equal the product of the correlation of item A with the true score (Rat) times the correlation of item B with the true score (Rbt). As the item-with-true-score correlations are assumed to be equal for all items, the products of Rat and Rbt is equal to the square of the item-with-true-score correlation for either of the items in question.

$$Rab= (Rat)(Rbt) = R^2at = R^2bt$$

These expressions denote the reliabilities of item A and B. The correlation of the scores for the two items (Rab) provides a method of estimating the reliabilities of Ra and Rb respectively. These interitem correlations help establish item reliability. Items which strongly correlate with one another are also more likely to strongly correlated with the true score of the unobserved variable of interest. These items are deemed to have greater discrimination. Discrimination is the defined as the strength of association between items and the true score. It is expressed as the correlation between items and the set of items as a whole i.e. item-to-total correlation.

CTT extends the concept of item reliability to that of scale reliability. Unidimensional items which measure the same underlying constructs form a scale. Scale reliability is measured by Cronbach's Alpha coefficient; this is the proportion of variance in a set of scores that can be attributed to a common influence on the scores of the individual items. The alpha coefficient emphasises the difference between the common variance and unique variance. When items are correlated with one another they share a commonality which gives rise to a correlation. Part of what determines the numeric value of one variable is related to part of what determines the numeric value of the other – that is the proportion of variability in each item that is associated with the variability in the other. This is the shared or common portion of each items variability. However, there is always some variation within items that is unrelated to other items; this is its unique variation. The greater the proportion of shared variation between two items the more they have in common and the more strongly they reflect a common true score. Cronbach's coefficient alpha is referred to as a measure of internal consistency reliability as it quantifies the degree to which a set of items share a common core of information about the same true score. A good Cronbach's Alpha value is considered to be higher than 0.7.

Temporal stability is also used to determine scale reliability using the test-retest measure. According to the principles of CTT if the stability of the true score of the variable of interest i.e. questionnaire item can be assumed, then changes in the observed score over time must be attributable to error. Therefore, a high correlation for scores across a specified time period would be indicative of low error and high reliability and conversely a low correlation for scores across a specified time period would indicate low reliability and substantial error.

Validity

Scale reliability is a precursor to scale validity. Scale reliability refers to the proportion of variance in a measure that can be ascribed to a common characteristic or theme shared by a group of items, whereas validity refers to whether that characteristic or theme is actually what is intended to be measured. The goals of determining scale validity are to provide evidence that the scope of the scale's items corresponds to the scope of the variable of interest and to demonstrate that the scores yielded by the scale are consistent with the broader understanding of how the phenomenon of interest varies in the real world.

There are a number of different ways in which validity can be measured during the development and assessment of a PROM, including, content validity and construct validity which includes convergent validity and known-groups comparison. Content validity ensures the PROM measures the concept of interest. This is usually established by patient and clinician testimony using qualitative methods. The content validity of LRRC-QoL was determined in Phase I of this project (Chapters 2-4).

Construct validity is tested by examining evidence the that scores on the PROM of interest conform to *a priori* hypotheses concerning logical relationships that are expected to exist with related measures such as existing PROMS or clinical measures. Convergent validity is a type of construct validity and assesses the extent to which a PROM relates to other measures based on theoretical content or the expected relationship with a chosen variable. Known groups validity is a second form of construct validity. Known groups validity statistically evaluates the differences between PRO scores and for groups of patients that differ by a known disease indicator i.e. disease severity.

7.3 Aims and Objectives

The overall aims of Phase III of this study were to determine the scale structure of the LRRC-QoL and to measure its psychometric properties, including:

- To test the hypothesised scale structure of the LRRC-QoL using the principles of multi-trait scaling analysis. This determined whether the items grouped together within the current, hypothesised scale were unidimensional and were therefore appropriately grouped.

- To identify any new potential scales, not previously identified using the principles of exploratory factor analysis.

- If new scales were identified, the scale structure of the LRRC-QoL was revised to incorporate the new scales. The unidimensionality of the revised scale structure of the LRRC-QoL was confirmed using the principles of multi-trait scaling analysis.

- To assess the psychometric properties of the finalised LRRC-QoL including reliability and validity.

The specific aims of this chapter are:

- To outline the methodology employed to determine scale structure of the LRRC-QoL
- To outline the psychometric methods employed to determine the reliability and validity of the LRRC-QoL
- To quantitatively assess the monthly recruitment rates for Phase III, including screened and recruited patients
- To determine the sociodemographic and clinical details of all responders.
- To determine any clinical differences between responders and non-responders

7.4 Methods

7.4.1 Cross-Sectional Observational Study

To assess the psychometric properties of the LRRC-QoL a cross-sectional observational study was undertaken. All eligible patients from participating centres were identified and invited to participate in the study. A self-complete questionnaire pack was sent to eligible patients. The pack included a Patient Information leaflet explaining the premise of the study, a consent form to agree to participation, a baseline demographics questionnaire, the LRRC-QOL tool, as well as additional quality of life measures including the EORTC QLQ-CR29 and FACT-C. A self-addressed stamped envelope was provided to return the questionnaire back to the clinical centre.

All patients were invited to participate in completing a second questionnaire pack 10-14 days following the return of the first questionnaire pack, thus enabling the investigators to carry out the test-retest test. This time interval between the two questionnaire packs was deemed sufficiently short

enough to ensure that clinical change in LRRC is unlikely to occur, but long enough to ensure that participants do not recall their responses from their first assessment. A short test retest interval is necessary to ensure stability is being evaluated, and not clinical change, which will underestimate reliability.

There is no formal sample size calculation for the development of PRO measures, however, recommended guidelines state 5-10 patients should be recruited per item within the questionnaire [212]. The proposed LRRC-QoL consists of 32 questions, therefore a sample size of 160 patients is deemed sufficient. With an estimated annual incidence of 700 new cases of LRRC in the UK [5], a sample of 160 is feasible to recruit.

Patients were sampled ensuring representation of patients with all patterns of disease recurrence (Table 7.1). Patient were identified from each LRRC pattern subset and approached to participate.

Table 7-1 Patient Sampling Representation For Field Testing

	No of patients per disease pattern of LRRC (Male: Female)			
	Anterior Recurrences	Central Recurrences	Lateral Recurrences	Posterior Recurrences
Completed Questionnaires	20:20	20:20	20:20	20:20

7.4.2 Recruitment

7.4.2.1 Eligibility

Inclusion Criteria

Patients were included in the study if the following criteria were fulfilled:

- aged ≥ 18 years
- with an existing resectable LRRC undergoing neoadjuvant treatment(s) **or**
- surgically treated for a LRRC within the last five years **or**
- had undergone non-surgical palliative treatment of LRRC **and**
- able to provide informed written consent to participate **and**
- able to read and write in English.

Exclusion Criteria

Patients were excluded from the study in any of the following criteria applied. They:

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

7.4.2.2 Patient Recruitment

Patients were recruited from the UK and Australia from the following sites:

- St James's University Hospital, Leeds, UK
- Royal Victoria Infirmary, Newcastle, UK

- Morriston Hospital, Swansea, UK
- St Marks Hospital, London, UK
- Southampton University Hospital, Southampton, UK
- The Royal Prince Alfred Hospital, Sydney, Australia
- Peter MacCallum Cancer Centre, Melbourne, Australia.

The principle investigator at each participating site identified potential patients using through three sources:

- Existing clinical registries
- New patient referrals through LRRC multidisciplinary team meetings
- Outpatient clinic setting.

7.4.2.3 Recruitment Log

A central recruitment log was kept at the two lead centres, Leeds and Sydney. This allowed for the regular review of screened, eligible and recruited patients

7.4.3 Data Collection

Data were collected on socio-demographic details, clinical details and PROMs.

Socio-demographic Data

Socio-demographic data fields were collected on patients' age, ethnicity, marital status, education and employment status. This data was captured utilising a self-complete baseline questionnaire by participants.

Clinical Data (Appendix 13)

The principal investigator for each site provided the following clinical details for each patient:

- Primary cancer details (location, neoadjuvant/adjuvant treatments, date of operation, operative and histological detail)
- Mode of detection of LRRC (symptomatic or surveillance)
- Pattern of recurrence (i.e. Anterior, Central, Lateral, Posterior)
- Treatment Intent (Curative/Palliative)
- Treatment plan of LRRC (pre-operative treatment, operative detail and histological detail, details of chemotherapy/radiotherapy)
- Presence of concurrent metastatic disease (i.e. lung, liver)

PROMs

Alongside the LRRC-QoL the EORTC QLQ-CR29 and FACT-C measures of HrQoL were included in the questionnaire pack. To minimise the potential for response bias the order of questionnaires was randomised on a 1:1:1 bias using a random sequence allocation.

- The LRRC-QoL (Appendix 12)

  The LRRC-QoL consists of 32 items and 5 proposed domains of symptoms, psychological well being, sexual function, future perspective and healthcare services.

- EORTC QLQ-CR29

  The EORTC QLQ-CR29 consists of 29 items making up 4 domains of urinary frequency, blood or mucus in stools, frequency of defaecation, body image and 29 single items. The EORTC QLQ-CR29 has been validated in patients with primary colorectal cancer undergoing a range of treatments and has displayed acceptable psychometric properties [285]. This measure has been used to document outcomes in patients with LRRC despite not being designed or validated for use in this cohort of patients[198, 324]. Previous work carried out as part of the LRRC-QoL Project identified the EORTC QLQ-CR29 covered 50% of the LRRC-specific domains (symptoms, sexual function, future perspective) and 33% of the LRRC-specific subdomains (pain and discomfort, urological symptoms, gastrointestinal symptoms,

sexual intercourse, mood, appearance and body image), thus making it a suitable PROM to use in this validation study.

- FACT-C

  The FACT-C consists of five subscales Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being and Colorectal Cancer Subscale. The measure has been widely validated for use in primary colorectal cancer and demonstrates acceptable psychometric properties [143]. It has been used in a number of studies to document outcomes in patients with LRRC [188, 191]. Previous work carried out as part of the LRRC-QoL Project identified the FACT-C covered 4 (66.6%) of the LRRC-specific domains (symptoms, psychological impact, role functioning and future perspective) and 7 (38.8%) subdomains (pain and discomfort, gastrointestinal symptoms, mood, work, social and relationships and future treatments), thus making it a suitable PROM for use in this validation study.

7.4.4 Data Analysis

All data were analysed using SPSS for Mac, version 22 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL). Data analysis was undertaken in a step-wise approach (Figure 7.1). Descriptive analyses of the demographic and clinical characteristics of all participants were performed.

7.4.4.1 Data Completeness

The completeness of data were analysed for LRRC-QoL to identify missing data at item and scale level, distribution of responses and floor/ceiling effects and descriptive analyses of items. Data completeness concerns the extent to which items are completed by the target population and the total number of available data sets from which total scores are computable [325]. The criteria for acceptable levels of missing data is <10% for items, <50% for computable total scale scores and for

maximum endorsement frequencies is <80% (floor/ceiling effects <80%) [326, 327]. Items which did not meet these predetermined criteria were discarded as it was deemed unlikely that these items would make valuable contributions to the underlying scale and the questionnaire overall, and would potentially contribute to a ceiling effect. Handling of missing data for each scale was conducted using simple imputation using half-mean imputation. If half or more of the items within the scale are complete, the missing items within the scale can be imputed with the mean of the remaining items. This is a valid and robust manner of missing data imputation for validating multi-item, multi-scale questionnaires [328, 329].

7.4.4.2 Scale Structure

The unidimensionality of the items within the proposed scales of the LRRC-QoL was assessed using the principles of multi-trait analysis and exploratory factor analysis. The combined results from these analyses informed the final structure of the LRRC-QoL.

Multi-Trait Analysis

Multi-trait scaling was used to determine whether the hypothesised items of the LRRC-QoL fit within the proposed scale structure. Pearson's correlation co-efficient of an item with its own scale and other scales was calculated. The grouping of items into subscales and scales and the calculation of summated scores was based on four scaling assumptions [330]:

1. Each item should have substantial correlation with the sum score computed from all the other items in that particular scale (item internal consistency).
2. Each item should have substantially higher correlation with the sum score of the rest of the items in the scale than with scales measuring other concepts (item discriminant validity).

3. For items in the same scale, the correlation between one item and the sum of the other items should be of similar magnitude for all items (equal item-to-total correlation).
4. Items in the same scale should have equal variance.

If the first and second criteria are fulfilled the current grouping of items is supported [331]. If the third and fourth criteria are fulfilled the items can be summed without weighting; if not, weighting is normally suggested to achieve equal item-to-total correlations and equal variances [331-333].

The multitrait/multi-item correlation matrix was used to examine the relationships of each item of the LRRC-QoL to its hypothesised scale. Each row in the matrix contains correlations between the score for one item and all hypothesised item groupings. Each column contains correlations between the score for one scale and all items in the matrix, including those items hypothesise to be part of that scale and those items hypothesised to be part of another scale. The multi-trait/ multi-item correlation matrix allows a number of assumptions to be examined simultaneously, including the assumption that items are substantially linearly related to the total scale score (item internal consistency) and that the items are stronger measures of their hypothesised constructs than of other constructs (item discriminant validity).

The item internal consistency was determined by measuring the item intercorrelation and the item-to-total correlation. The item intercorrelation measures the extent to which the items are related and should be between 0.3 and 0.7. The item-to-total correlations are a measure of the item convergent validity and indicate the strength of the relationship between the individual items and the construct being measured. The recommended value of item-to-total correlation values is 0.3.

Item discriminant validity gauges the extent to which items correlate more highly with the concept they are hypothesised to represent than with other concepts. Item discriminant validity is supported and a scaling success declared when the correlation for an item and its hypothesised scale is more than two standard errors higher than its correlations with another scale [332, 333]. Item discriminant validity is also supported when correlations of <0.4 are observed between an item and other scales in the questionnaire.

A definite scaling error occurs when the correlation of an item with another scale exceeded the correlation with its own scale by two standard errors. A probable scaling error was considered to be present when a correlation between an item and another scale exceeded the correlation with its own scale, but by less than two standard errors.

Exploratory Factor Analysis

The aim of running an exploratory factor analysis (EFA) on the LRRC-QoL questionnaire was to test the scale structure and stability by identifying clusters of items which were not previously hypothesised into a scale. EFA summarises the correlations amongst items in terms of underlying dimensions or factors. Items which correlate highly together will load onto the same factor. There are two main components to EFA, which include, estimating the number of underlying dimensions and rotating the number of factors to identify which items cluster on the same factor.

EFA will be conducted in a step-wise fashion. Firstly, the suitability of the data for EFA will be determined using the Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy and Bartlett's Test of Sphericity. The KMO index ranges from 0 to 1, with an index measure of 0.50 and above considered suitable for factor analysis. The Bartlett’s Test of Sphericity should be significant (p <0.05) for factor analysis to be suitable.

On determining the suitability of the data for EFA the next stage of the analysis was to determine how the factors were extracted. For the LRRC-QoL principal component factor analysis with oblique rotation was used. The oblique rotation method was chosen as it allows for correlation between factors. Factors were extracted based on the following pre-requisites:

- A eigenvalue of greater than 1.00
- Cumulative percentage of variance – each component has to account for at least 5% of the variance amongst items.
- Appropriate examination and interpretation of Scree plots. The scree plot is a graphical representation of the eigenvalues for all the extracted factors. The plotted eigenvalues are examined to determine where a natural break point occurs in the data and the curved line flattens out. The number of data points above the break are indicative of the number of factors which should be retained.

7.4.4.3 Scale Reliability

Reliability is the degree to which the questionnaire is free from random error this is measured by the internal consistency of a scale and reproducibility of the questionnaire using the test-retest measure.

Internal consistency measures the homogeneity of a scale ensuring all items are sufficiently similar, thus ensuring scale reliability using alpha coefficients (Cronbach's Alpha). Cronbach's Alpha indicates the extent to which items in a scale are interrelated by comparing the variance of the total score to the sum of the variances of the individual items. As the correlations between the items increase, the variance for the total score increases and alpha coefficients approximate unity. Internal consistency is considered to be good when Cronbach's alpha co-efficient exceeds 0.70. Cronbach's

Alpha were calculated for all the finalised scales of the LRRC-QoL, along with 95% confidence interval values.

The results from exploratory analysis were used to determine whether the sample size used to conduct the psychometric analysis was appropriate to conduct Cronbach's Alpha. The eigenvalues from the principle component analysis were examined, if the first eigenvalue was >3 the sample size was deemed satisfactory [334]. Similarly, if the component pattern for the factor loadings was stable, with factor loadings of >0.6 for at least four variables within each factor [335], the sample size was deemed adequate to conduct reliability analysis using Cronbach's Alpha.

The test-retest measure assesses the stability of the questionnaire over a period of time during which the patients clinical state remains stable. The Intraclass coefficient (ICC) was used to measure the strength of agreement between repeated measures, by assessing the proportion of total variance of an observation that is associated with the in-between patient variability. If the ICC is large this suggests the random variability is low and a high proportion of the variance is attributable to the variation between patients. The measurements are thus described to have high reliability. Conversely, if the ICC is low, the random error variability dominates and the measurements have low reliability. An ICC score of 0.7 or above is recommended to ensure good test-retest reliability. The ICC was calculated using a fixed effects analysis of variance (ANOVA) model[336] and reported along with 95% confidence interval values.

7.4.4.4 Validity

Construct Validity

Construct validity can be assumed when the second round of multitrait scaling analysis on the LRRC-QoL produces the same or similar underlying factor structure.

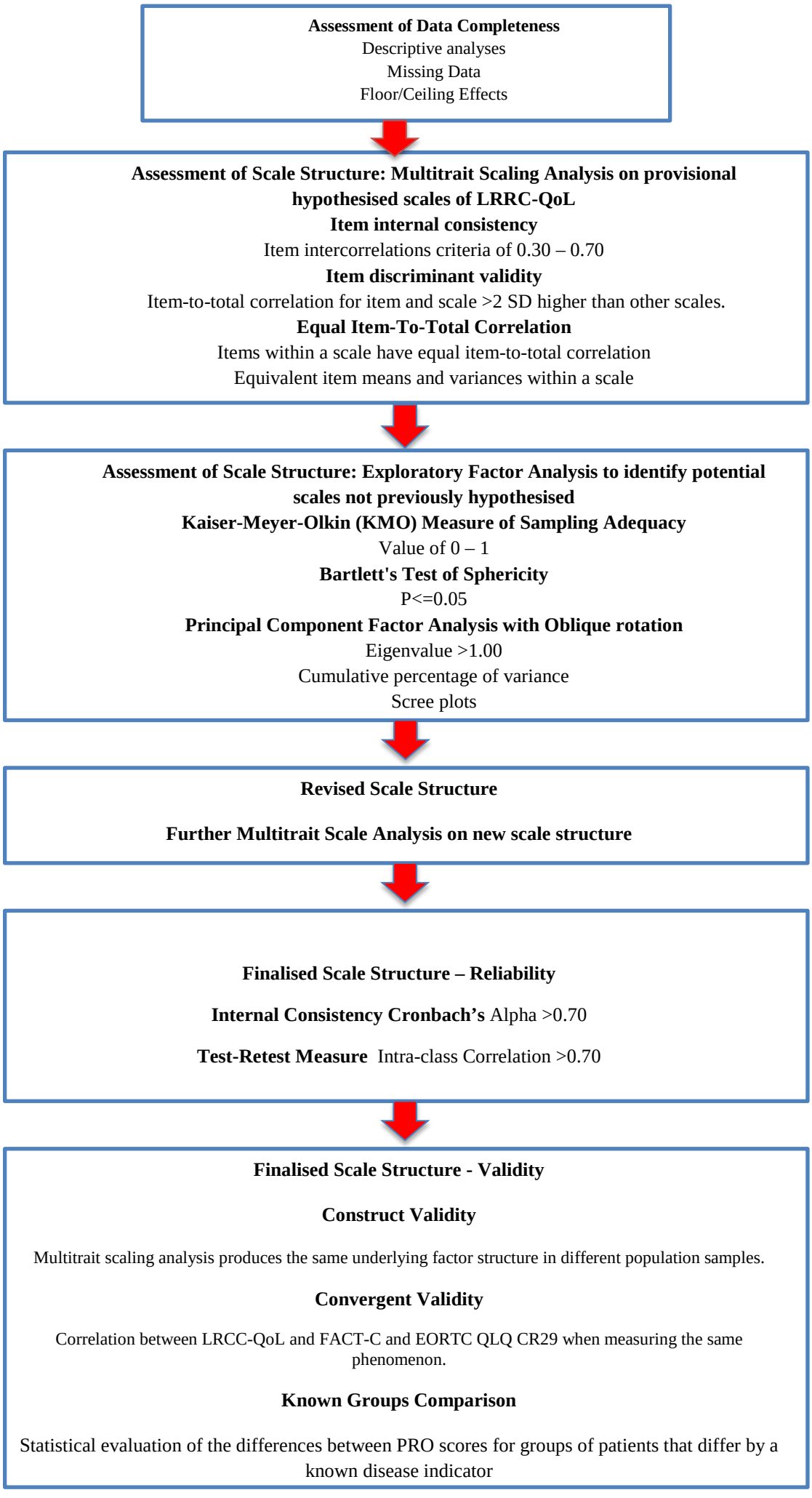
Convergent Validity

Convergent validity reflects the correlation between individual assessment tools measuring the same phenomenon. Convergent validity was evaluated by making comparisons between the LRRC-QOL and the FACT-C and EORTC QLQ CR-29 questionnaires. Both of these questionnaires have been used in previously in studies in patients with LRRC. Pearson's product moment correlation was used to analyse correlation between the items and scales of the LRRC-QoL, EORTC QLQ CR29 and FACT-C. Pearson's values of greater than 0.45 are considered to be highly correlated. It was hypothesised that the scales in the LRRC-QoL will not correlate with the FACT-C and EORTC QLQ-CR29 unless they address similar themes.

Known-Groups Comparison

The method of known-groups comparison was used to assess the ability of the LRRC-QoL to distinguish between patients differing in clinical status. The clinical parameters hypothesised to form mutually exclusive patients for subgroup comparison included disease stage (local recurrence versus local recurrence and metastatic disease), recurrent disease location (central, anterior, lateral or posterior), treatment intention (curative versus palliative) and pre-operative treatments (chemoradiation versus none). The independent student t-test was used to examine differences in mean scores in 2 groups and the one way analysis of variance (ANOVA) for more than 2 groups.

Figure 7-1 Overview of Step-Wise Data Analysis Plan



7.4.4.5 Sample Size Justification

The sample size for the LRRC-QoL was based on previous guidance from the EORTC, which recommends a subject to item ratio of 5-10 participants per item [212]. Based on the hypothesised LRRC-QoL having 32 items a sample size of 160 was calculated, however, for the purposes of this thesis, an interim analysis on the British cohort was conducted in a sample size of 80 patients. A number of analyses were conducted to determine whether the results obtained from the psychometric analysis from the British LRRC-QoL cohort were reliable given the potential limitations engendered by our small sample size.

Key components of exploratory factor analysis were examined to determine whether the sample size included in the final analysis was adequate. This includes assessing the following:

- Communality of the variables

  The communality measures the percentage of variance in a given variable explained by all the factors jointly and may be interpreted as the reliability of the indicator. High communalities indicate that the recovery of population factors in the sample data is good, irrespective of the sample size [337, 338]. It is recommended that the communalities should all be greater than 0.6 or the mean level should be at least 0.7 [339].

- Degree of overdetermination of the factor

  Overdetermination is the factor to variable ratio. Six variables per factor combined with a small number of factors is considered to be high overdetermination of factors if the majority of communalities are <0.50 [339]. A minimum of 3 variables is required per factor, a factor with fewer variables than this is considered to a weak

factor [337, 338].

- Size of Loading

  Factor loading is the correlation between a specific observed variable and a specific factor. Factor loadings of >0.6 are considered to be high. Five or more strongly loading items (>0.50) are desirable and indicate a robust factor. However, if factors possess four or more variables with loadings above 0.60, this is also acceptable. There should be few item crossloadings. A crossloading is when an item loads at 0.32 or higher on two or more factors [337]. A low number of crossloadings enables each factor to be defined by a distinct set of interrelated variables.

To interpret estimates of reliability and validity 95% confidence intervals were reviewed for all Cronbach's Alpha, IntraClass correlation and Pearson product moment correlation co-efficient values. The size of the confidence intervals indicates the precision of the underlying value, with narrow confidence intervals associated with greater precision. The range of values included in the confidence intervals indicate plausible values for the true reliability and validity values.

7.5 Results

7.5.1 Recruitment

A total of 206 questionnaire packs were sent to 5 UK centres over a 22 month period between January 2015 and September 2016. Two centres failed to recruit any patients, one due to non-engagement in the recruitment phase and the second due to lengthy internal R&D set-up. Two of our five sites were open within the first 7 months of the study, with our third and fourth sites opening at 8 and 11 months following the opening of the first site. Due to

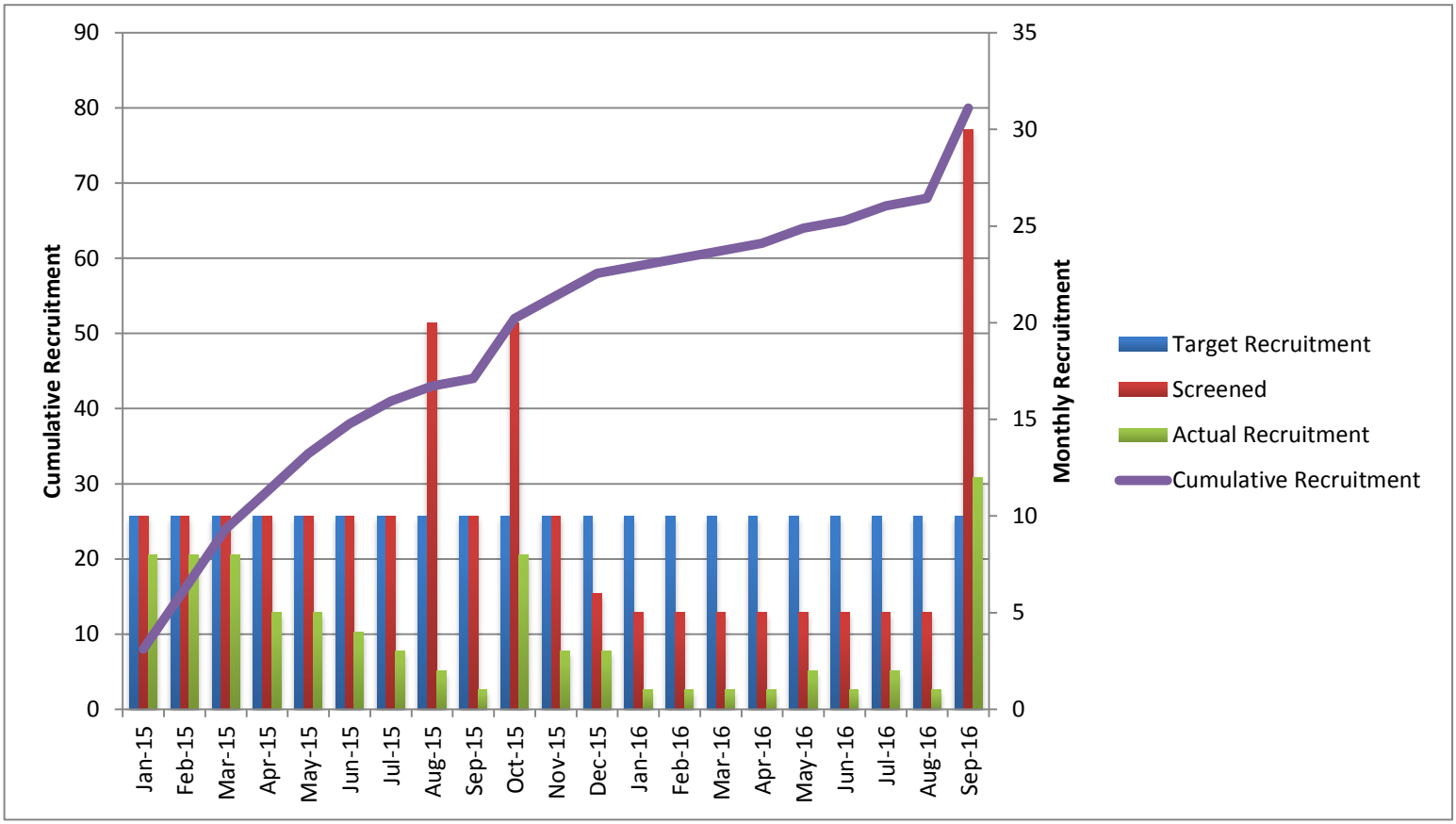
significant delays and difficulties at local level we failed to open our 5th site. The original recruitment target was 10 patients per month with a total recruitment period of 8 months, however, we failed to achieve this target in a timely fashion achieving 80 patients in 21 months.

There were significant difficulties with the Australian recruitment. This included significant delays in obtaining ethical approval in Australia. Furthermore, a number of concurrent studies were identified by the Australian investigators examining PROs in patients with locally advanced pelvic oncology, including LRRC, which employed a number of questionnaires. This unfortunately led to a patient complaint regarding high responder burden due to the co-enrolment into multiple studies. Consequently, an executive decision was made by the clinical research team to delay the commencement of LRRC-QoL until the completion of conflicting studies. Given these constraints the recruitment of Phase III did not start at the same time as the British recruitment. Therefore, a pragmatic decision was made to delay the Australian recruitment until the completion of the current, on going clinical studies, in order to maximise recruitment and to conduct an initial interim analysis on the UK cohort, followed by a complete analysis upon completion of the Australian recruitment. The results from this chapter concentrate primarily on the UK recruitment of Phase III.

Ten patients were screened per month on average, during the first half of the recruitment phase however, this fell to half during the second half of the study as demonstrated by the recruitment chart (Figure 6.2). There were three spikes in the screening rates of patients in August 2015, October 2015 and September 2016. The first two screening spikes corresponded with the opening of two new sites during the course of the study. The first spike in screening rates in August 2015 failed to convert to a spike in the recruitment phase. This was due to the non-engagement with recruitment by the clinical team and the principal investigator at this

site. The second spike in screening rates in October 2015 led to an increase in recruitment rates for that month. However, following this increase recruitment fell back to recruiting 1-3 patients/month. The final spike in screening was due to a targeted screening strategy employed at two centres, Leeds and Newcastle, to help identify potentially eligible patients. During this month patients' were personally identified by the Chief Investigator by examining MDT records, outpatient clinic lists and theatre operating lists. Access to in-house clinical registries was provided during this timeframe which further helped identify potential patients. During this final screening spike patients were personally approached for participation of the study. This targeted recruitment strategy led to an increase in recruitment rates and enabled the study team to reach the final recruitment target.

Figure 7.2 Recruitment Graph for Phase III LRRC-QoL



7.5.2 Patient Demographics

Responder Demographics

Of the 206 questionnaires sent 80 (38.8%) patients responded to the LRRC-QoL questionnaires. Of these 80 patients, 54 (67.5%) participated in the second round of the LRRC-QoL questionnaire testing. All patient demographics and clinical details are highlighted in Table 7.2. Sixty-one male and 19 female patients, with a median age of 66 years participated in the study. Forty patients with a gastrointestinal stoma and 6 patients with a urostomy participated in the study. Thirty seven patients were treated with curative intent and 21 patients were treated with palliative intent. A total of 35 (43.8%) of patients underwent operative intervention, of which only one patient underwent surgical intervention for palliation of symptoms. The current disease status was disease free in 22 (27.5%) patients, distant disease recurrence in 3 (3.8%) patients and local disease recurrence in 12 (15%). The disease status is unknown in 43 (53.8%) of patients.

Responder vs. Non-Responders: Patient and Clinical Demographics

The rate of missing data for the clinical categories was variable, ranging from 3.9-20.9% in the responder group and 5.6-43.7% in the non-responder group. Personal information regarding ethnic group, marital status, educational status was unavailable for the non-responder group as this is data that is not routinely captured in clinical practice and was obtained using a self-completed form in the LRRC-QoL questionnaire pack. On comparing patient and clinical variables between responders and non-responders it was noted that responders were older in age (62 vs. 58, p=0.01) and male (61 versus 46, p=0.01) (Table 7.2). Non-responders were more likely to have their LRRC treated with palliative intent (19.9% vs. 10.2%, p=0.03) and to have distant metastatic disease (3.4% vs. 1.5%, p=0.02). A range of operation types were undertaken in both groups, with no demonstrable differences between the two cohorts. However, despite the heterogeneous nature of the operative interventions

undertaken, both groups of patients were similar with regards to LRRC disease subsite. Furthermore, there were no differences between the two groups with regards to mode of detection of LRRC and presence of concurrent metastatic disease.

Table 7-2 Patient and Clinical Demographics

Variable	Responders N = 80	Non - Responders N=126	P Value
Patient Demographics			
Gender			
Male: Female : Unknown	60:20:00	46:34:46	0.01
Mean Age (SD)	66 (8.05)	58 (12.27)	0.01
Ethnic Group			
White	69 (86.3)	Unknown	N/A
Black	5 (6.3)	Unknown	
Asian	1 (1.3)	Unknown	
Unknown	5 (6.3)	Unknown	
Marital Status			
Married	62 (77.5)	Unknown	N/A
Living Common Law	5 (6.3)	Unknown	
Widowed	3 (3.8)	Unknown	
Separate	2 (2.5)	Unknown	
Divorced	1 (1.3)	Unknown	
Single	1 (1.3)	Unknown	
Unknown	6 (7.5)	Unknown	
Education Status			
Secondary School	30 (37.5)	Unknown	N/A
College	20 (25.0)	Unknown	

University	20 (25.0)	Unknown	
Other	3 (3.8)	Unknown	
Unknown	7 (8.8)	Unknown	
Employment Status			
Self-employed	12 (15.0)	Unknown	N/A
Home maker	0 (0.0)	Unknown	
Full Time Employment	2 (2.5)	Unknown	
Part Time Employment	4 (5.0)	Unknown	
Unemployed	1 (1.3)	Unknown	
Sick Leave	9 (11.3)	Unknown	
Retired	44 (55.0)	Unknown	
Unknown	8 (10.0)		
Years Between diagnosis of Primary Rectal Cancer and LRRC			
1	12 (15.0)	15 (11.9)	
2	20 (25.0)	26 (20.6)	
3	12 (15.0)	19 (15.0)	
4	5 (6.25)	11 (8.7)	0.72
5	4 (5.0)	1 (0.79)	
6	7 (8.75)	8 (6.3)	
Unknown	20 (25.0)	46 (36.5%)	
Primary Rectal Cancer Details			
Neoadjuvant Treatment			
None	31 (15.0)	36 (17.5)	
Chemoradiation	22 (10.7)	36 (17.5)	
Short Course Radiotherapy	3 (1.5)	4 (1.9)	0.3
Contact Radiotherapy	1 (0.5)	0 (0.0)	
Unknown	23 (11.2)	50 (24.3)	

Operation			
Anterior Resection	37 (18.0)	42 (20.4)	
APER	9 (4.4)	15 (7.3)	
Composite Abdominosacral Resection	2 (1.0)	1 (0.5)	
Hartmann's	6 (2.9)	12 (5.8)	0.54
Panproctocolectomy	0 (0.0)	3 (1.5)	
Pelvic Exenteration	1 (0.5)	2 (1.0)	
Local Excision	3 (1.5)	1 (0.5)	
Unknown	22 (10.7)	50 (24.3)	
Dukes Stage			
A	11 (5.3)	9 (4.4)	
B	20 (9.7)	18 (8.7)	0.05
C	26 (12.6)	41 (19.9)	
D	1 (0.5)	1 (0.5)	
Unknown	22 (10.7)	57 (27.7)	
Margin Status			
R0	50 (37.5)	63 (47.4)	
R1	8 (6.0)	11 (8.3)	0.66
R2	0 (0.0)	1 (0.8)	
Unknown	22 (27.5)	51 (40.4)	
Adjuvant Chemotherapy			
Chemoradiation	3 (1.5)	3 (1.5)	
Chemotherapy	31 (15.0)	38 (18.4)	
Short Radiotherapy	0 (0.0)	1 (0.5)	0.33
None	24 (11.7)	33 (16.0)	
Unknown	22 (10.7)	51 (24.8)	

Locally Recurrent Rectal Cancer Details			
Mode of Detection			
Surveillance	46 (22.3)	62 (30.1)	0.19
Symptomatic	12 (5.8)	14 (6.8)	
Unknown	22 (10.7)	50 (24.3)	
Pattern of Recurrence			
Anterior	5 (2.4)	12 (5.8)	
Central	22 (10.7)	22 (10.7)	0.07
Lateral	19 (9.2)	17 (8.3)	
Posterior	12 (5.8)	26 (12.6)	
Unknown	22 (10.7)	49 (23.8)	
Presence of Metastatic Disease			
Yes	11 (5.3)	14 (6.8)	
No	47 (22.8)	62 (30.1)	0.20
Unknown	22 (10.7)	50 (24.3)	
Treatment Intent			
Curative	37 (18.0)	36 (17.5)	
Palliative	21 (10.2)	41 (19.9)	0.03
Unknown	22 (10.7)	49 (23.8)	
Palliative Treatment			
Chemotherapy	16 (24.2)	30 (48.4)	
Chemoradiation	4 (6.5)	8 (12.9)	0.65
Radiotherapy	0 (0.0)	1 (1.6)	
Surgery	1 (1.6)	0 (0.0)	
Pre-operative Treatment			
None	9 (12.5)	19 (26.4)	
Chemotherapy	1 (1.4)	2 (2.8)	

Chemoradiation	18 (25.0)	12 (16.7)	0.09
Radiotherapy	2 (2.8)	0 (0.0)	
Unknown	5 (6.9)	4 (5.6)	
Margin Status			
R0	21(29.6)	19 (26.8)	
R1	13 (18.3)	15 (21.1)	0.75
R2	1 (1.4)	2 (2.8)	
Post-Operative Treatments			
Chemotherapy	8 (10.5)	8 (10.5)	
None	27 (35.5)	27 (35.5)	1.00
Unknown	3 (3.9)	3 (3.9)	
Current Disease Status			
Disease Free	22 (10.7)	21 (10.2)	
Distant Disease Recurrence	3 (1.5)	7 (3.4)	0.02
Local Disease Recurrence	12 (5.8)	8 (3.9)	
Unknown	43 (20.9)	90 (43.7)	
Operation Type			
Composite Abdominosacral Resection	6 (7.8)	5 (6.2)	
Anoproctectomy	1 (1.3)	3 (3.9)	
Abdominoperineal Excision of Rectum	7 (9.2)	4 (5.3)	
Abdominoperineal Excision of Rectum with partial vaginectomy	0 (0.0)	2 (2.6)	
Resection of mass	5 (6.5)	8 (10.4)	
Resection of mass with en bloc small bowel resection	1 (1.3)	1 (1.3)	
Resection of mass en bloc hysterectomy/BSO	1 (1.3)	1 (1.3)	
Resection of mass with en bloc small bowel, and proctectomy	0 (0.0)	1 (1.3)	
Resection of mass with en bloc vaginectomy	1 (1.3)	1 (1.3)	

Excision of mass with partial cystectomy, distal uretectomy and reimplantation	0 (0.0)	1 (1.3)	0.07
Excision of neorectum and segment 6 metastatectomy	1 (1.3)	0 (0.0)	
Hartmann's	3 (3.9)	1 (1.3)	
Hartmann's with en bloc hysterectomy, bilateral salphino-oopherectomy, left ureterectomy and resection of pelvic side wall mass with reimplantation of ureter	0 (0.0)	1 (1.3)	
Laparotomy and bypass of recurrent rectal cancer	1 (1.3)	1 (1.3)	
Pelvic Exenteration	1 (1.3)	3 (3.9)	
Proctectomy	0 (0.0)	2 (2.6)	
Proctectomy with en bloc resection of cervix	1 (1.3)	0 (0.0)	
Resection of neorectum	1 (1.3)	0 (0.0)	
Resection of neorectum and en bloc hysterectomy	0 (0.0)	1 (1.3)	
Resection of recurrent mass with en bloc psoas muscle and iliacus	1 (1.3)	0 (0.0)	
Transacral excision of mass	3 (3.9)	1 (1.3)	
Ultralow AR with loop ileostomy with en bloc resection of R obturator node	1 (1.3)	0 (0.0)	

7.6 Discussion

Conducting multi-centre research has a number of challenges at a number of different time points during the course of a study, which are further amplified on an international platform. Recruitment to the LRRC-QoL has been long, difficult and challenging. We were unable to recruit to LRRC-QoL in the pre-specified timeframe. However, due to the constant review of recruitment strategies the target recruitment was eventually reached for the British cohort of patients.

Delays during the initial phases of site set up were attributable to the difficulties in obtaining local Research and Development approval from each individual participating NHS trust, most of which have individualised and lengthy review processes [340-342] Further ethical approval had to be sought from the Australian Ethics Committee and the local ethics approval board which led to significant delays in commencing the final phase of the LRRC-QoL in Sydney and Melbourne. Furthermore, a number of on going, competing studies were identified at the Australian centres. Co-enrolment of patients into studies can be employed as a strategy to maximise recruitment in difficult disease settings [343]. Although, there are no regulatory prohibitions on co-enrolment of patients into more than one study, there are ethical and statistical concerns regarding co-enrolment [344]. From an ethical perspective there are often concerns regarding patient burden when participating in multiple studies. From a statistical perspective co-enrolment into two studies can potentially lead to interactions between the two studies, which can have an impact on the obtained results. Given these ethical and statistical concerns of co-enrolment and the patient complaint, co-enrolment was not pursued as a recruitment strategy for LRRC-QoL. The concept of co-enrolment was not pursued in the UK, as there were no other conflicting studies identified during the study period.

Timely and adequate recruitment of eligible participants is often a key challenge when conducting research in the advanced malignancies and rare disease settings due to a multitude of reasons. The key contributing factor for this is that the overall pool of potentially eligible patients in these complex disease settings are often small, which is further attenuated when applying stringent eligibility criteria. Further compounding this is the comparatively higher refusal rate by eligible patients and greater professional 'gate-keeping' of access to patients [345]. This can potentially have an impact on the results obtained as high refusal rates have an effect on sample bias, which can limit the generalisability of the results. A further barrier to recruitment in advanced cancer is patient illness, with severity of illness correlating with reduced research participation [346]. Amongst, this cohort of patients, there is also a higher

rate of attrition due to their unpredictable health status. Our study reflects this as a significantly higher proportion of patients who were treated with palliative intent and patients who went on to develop metastatic disease declined participation into the study.

LRRC is a relatively rare occurrence in the modern management of primary rectal cancer, occurring in 5-10% of patients treated for primary rectal cancer, with approximately 700 patients a year treated operatively within the UK [5]. Due to this relatively small patient population, a number of strategies were employed in a bid to maximise recruitment. The LRRC-QoL was designed as a multi-centre collaborative project in a bid to maximise the potential pool of eligible patients across the UK and Australia. Centres with an established practice in LRRC, a track record of research in this setting, and an established clinical registry were approached and recruited to the study prior to the commencement of Phase III. The overall eligibility criteria was kept broad to include all patients with LRRC, irrespective of disease recurrence subsite, current disease status or treatment strategy. The overall burden of participation was kept to a minimum and patients were specifically asked whether they wanted to continue their participation in the project by completing a second questionnaire.

Often within the context of multicentre research there are a number of healthcare professionals involved, including surgeons, oncologists, nurse specialists and clinical research fellows, who act as 'gatekeepers' for patients. This can make access to potential participants a convoluted process requiring multiple communication systems to ensure appropriate access to potentially eligible patients. Furthermore, the involvement of multiple teams, both central and locally can make it difficult to monitor the project overall to identify practical and logistical difficulties and appropriate solutions. In an attempt to reduce professional gate-keeping and to reduce local investigator burden, the central research team kept in regular contact with all participating sites attempting to identify any potential problems and to offer

solutions and support. Furthermore, the central research team attempted to obtain access to the LRRC clinical registries at each site to help identify potentially eligible patients and to coordinate this centrally. Of the 4 participating sites, only 2 sites (Leeds and Newcastle) were able to provide on-site access to the clinical registries following local approval. Open access to these registries allowed for the rapid identification of potentially eligible patients, the acquisition of relevant clinical and operative data and improved overall recruitment rates.

The use of clinical registries and patient advocacy groups have been utilised in aiding recruitment, developing and validating PROMs in rare disease settings [347-350]. However, gaining access to such registries is a long and difficult process, requiring further local approvals. The use of a patient advocacy group was not employed to help aid the recruitment to phase III, as there are no established patient groups specifically for LRRC. Although the use of such groups may potentially increase the overall recruitment pool, it may cause potential issues, with regards to the acquisition of relevant clinical details to enable appropriate context in which to interpret any obtained PROs. The use of patient advocacy groups may not be appropriate to recruit patients during the validation phase of a PROM however it would be ideally suited to promote the use of a future PROM.

To help maximize recruitment a number of strategies were employed. Personalised letters addressing the patient themselves from the lead PIs were sent to all patients from collaborating centers. In combination with this centers were emailed for monthly updates to identify screened and recruited patients. Site visits were arranged to help engage local investigators at the three main recruiting sites, Leeds, Newcastle and Swansea. To reduce local investigator burden a pragmatic decision was made not to send reminder letters. This was primarily due to the fact that some of the local investigators found it difficult to send out

a second questionnaire at the two week interval following the receipt of the first questionnaire from responders as well as sending out a reminder questionnaire to the non-responders.

A number of recruitment strategies have been investigated previously in a bid to identify methods of improving response rates to postal questionnaires. The use of monetary incentives, shorter questionnaires, coloured ink, personalised letters, the use of stamped addressed envelopes, questionnaires sent by first class post, contacting participants prior to sending questionnaires providing non-respondents with follow up questionnaires are all strategies associated with improved response rates [351-353]. The LRRC-QoL employed a number of these strategies in an attempt to maximise recruitment, this included designing the project as a multi-centre, collaborative project, employing broad eligibility criteria, regular communication between the coordinating site and peripheral sites, local site visits, the use of stamped addressed envelopes, the use of first class postage and sending out personalised letters from the PIs to patients. However, despite these efforts our overall response rate was low.

Our response rate of 38.8% is much lower than previous reported response rates of 52.5 – 74.9% in studies collecting PROs and HrQoL data in patients with primary colorectal cancer [354, 355]. However, our response rates are similar to observed response rates of 40-46.7% in patients with metastatic colorectal cancer [356, 357]. It is likely these lower response rates in metastatic and recurrent colorectal cancer are a reflection of the disease status of this cohort of patients, making them less likely to engage in research due to ill health. This is further reflected in the patient and clinical demographics of the patients who refused participation in this study, with a higher proportion of patients treated with palliative intent and disease re-recurrence refusing participation. Other key differences between the responder and non-responder group were gender and age, with a higher proportion of male and older patients

consenting to participate in the study. These key differences between the responder and non-responder groups have important implications on the validation of the LRRC-QoL, as the study population does not accurately reflect the patient and clinical demographics of the wider population affected with LRRC, thus potentially reducing the generalisability of the obtained results. As this study only validates the results obtained from the UK cohort of patients, it will be essential to appropriately monitor the sample characteristics of the Australian cohort to ensure a more broad and wider range of patients are targeted. This should include female patients, younger patients and those treated with palliative intent, to ensure the overall sample is representative of the intended population

There are no formal sample size calculations for the development and validation of PROMS [358]. There are however, a number of methods which have been employed in determining a sample size in the validation of PROMS, this includes an arbitrary minimum sample size, a subject to item ratio and a subject to item ratio with *a posteriori* justification [358]. The subject to item ratio is the most frequently recommended method of sample size determination when employing exploratory factor analysis. However, there are a number of conflicting guidelines on the optimal sample size when conducting exploratory factor analysis, with values ranging from 100 – 1000 [359-361]. These arbitrary guidelines have been appropriately criticised as they do not reflect the often complex dynamics of factor analysis. It is the underlying strength of the data, which determines the robustness of the exploratory factor analysis. The strength of the data is assessed by high item communalities and several variables loading onto each factor [338]. Using these principles small sample sizes of 50 are appropriate for exploratory factor analysis in determining the scale structure of a PROM [362]. To mitigate the impact of having a relatively small sample size key components of exploratory factor analysis were analysed in an attempt to justify the sample size used and ensure potentially meaningful data had been obtained from the analysis. By closely examining

the communality of the items, degree of overdetermination of the factor and the size of the loading, we were able to determine whether our sample size was adequate.

The overall small sample size can limit the generalisibility of the results and the precision of the estimates of reliability and validity of the measure overall. Previous sample size requirements stipulated to provide reliable and precise estimates of Cronbach's Alpha include Nunally's recommendation of a minimum sample of 300 patients [363]. However, in practice, such sample sizes are often not achieved. Recent works have focused on the use of smaller sample sizes and determining precise measures of reliability by using the eigenvalue values of principal component analysis and through the reporting of confidence intervals [334, 364]. Yurdugul et al demonstrated that if the value of the first eigenvalue is >6 the observed value of Cronbach's alpha is a robust estimate of the population Cronbach's Alpha, even when the sample size is limited to 30 patients [334]. Similarly, if the first eigenvalue is 3-6 a required minimum sample size of 100 patients is adequate to demonstrate an unbiased estimate of reliability [334].

To determine the precision of the results obtained from the measures of reliability (Cronbach's Alpha and Intra-class coefficient) and validity (Pearson's product moment correlation) the 95% confidence intervals were reported. Narrow confidence intervals indicate a more precise estimate for the observed value compared to wider confidence intervals. On assessing confidence intervals for reliability, in particular for Cronbach's Alpha, the confidence intervals are wider for observed values which are low, and narrow as the value gets closer to 1.0, irrespective of the number of items included in the scale [364]. The sample size impacts upon the confidence intervals obtained for both Cronbach's Alpha and the IntraClass correlation, with wider values observed in smaller sample sizes [365]. The precision of the value of Cronbach's Alpha is affected by the sample size, the number of

items within a scale and the individual item intercorrelations. As the number of items increase within a scale, the strength of the Cronbach's Alpha value increases, with the narrowing of the associated confidence intervals. A similar relationship is observed for item intercorrelations. As the strength of the item intercorrelations increase, the Cronbach's Alpha value increases and the width of the confidence interval decreases. The relationship between sample size and the precision of Cronbach's Alpha is slightly more complex. Confidence intervals are wide for small sample sizes, however, confidence intervals are also affected by the value for item intercorrelation and number of items so that confidence interval widths can be similar for example when sample sizes range from small (n=30) to large (n=200) when the value for item intercorrelation is >0.6 in a scale consisting of 2 items, or a item intercorrelation value of >0.4 in a scale consisting of 5 items [364, 365]. Similar principles apply to determining the precision of validity by examining the associated confidence intervals reported with Pearson's product moment coefficient. Wider confidence intervals are observed with low validity irrespective of sample size [365].

7.7 Conclusion

This chapter outlines the methodology employed to determine the scale structure of the LRRC-QoL and the psychometric methods to assess the reliability and validity of the LRRC-QoL. The chapter highlights the recruitment of Phase III for the UK cohort and compares clinical characteristics between responders and non-responders

8 Chapter 8 – Psychometric Analysis of the LRRC-QoL

8.1 Introduction

Chapter 7 highlights the methodology employed to validate the LRRC-QoL and documents the recruitment rate to Phase III in the UK cohort. This chapter reports on the results of the psychometric analysis of the LRRC-QoL; reporting on the final scale structure and the overall reliability and validity of the LRRC-QoL in the UK patient cohort.

8.2 Aims and Objectives

The overall aims of Phase III of this study were to determine the scale structure of the LRRC-QoL and to measure its psychometric properties. The specific aims and objectives are outlined in Chapter 7.3.

8.3 Results

8.3.1 Data Completeness

Table 8.1 and 8.2 present the descriptive analyses of the data at an item and scale level respectively. Overall, the quality of the collected data was good, with total computable score range of 88.7 – 100%. Missing data were higher for questions of a personal nature. The sexual function scale had the lowest computable score and the highest missing data rate at item level. Similarly, questions regarding gynaecological symptoms (items 5 and 6) had a higher missing data rate of 15%.

The criteria for acceptable levels of missing data is <10% for items and < 50% for computable total scale scores, with maximum endorsement frequencies of <80% (floor/ceiling effects <80%) [326, 327]. A number of the LRRC-QoL items did not fulfil these criteria (Table 8.2). For the symptoms scale, items 5 and 6 regarding gynaecological symptoms had a missing data rate of 20% at item level however, the total computable scale score for the scale was 100%. The sexual function scale also had considerably higher levels of missing data at item level compared to the other scales of LRRC-QoL, with a range of 15-26.3%. All these items address a range of issues which are of a personal nature and therefore the rate of missing data is not unsurprising. Given the importance of these items identified during the qualitative phase of the project a pragmatic decision was made to include all these items within their relevant scale.

The only item which failed to meet a maximum endorsement rate of <80% for a response category was item 14, regarding management of a urostomy, having a maximum endorsement rate of 100% for the response category option 3. Consequently, this item was excluded from the LRRC-QoL, due to potential ceiling effects.

The psychological function scale, future perspective scale and healthcare services scale all fulfilled the pre-requisite criterion at an item and scale level and were therefore appropriately included for further analyses.

Table 8-1 Item Level Descriptive Analyses for Hypothesised LRRC-QoL

Symptom Scale	N	Missing (%)	Mean	Std. Deviation	Response Value Frequency			
					1	2	3	4
1. Abdominal Pain	80	2 (2.5)	1.62	0.669	37 (46.3)	35 (43.8)	5 (6.3)	1 (1.3)
2. Back Pain	80	0 (0.0)	1.89	0.900	32 (40.0)	30 (37.5)	13 (16.3)	5 (6.3)
3. Perianal/Buttock Pain	80	1 (1.3)	1.92	0.958	31 (38.8)	31 (38.8)	9 (11.3)	10 (10.4)
4. Rectal Bleeding/Discharge	80	1 (1.3)	1.56	0.813	1 (49.0)	18 (22.5)	10 (12.5)	2 (2.5)
5.Vaginal Bleeding or discharge*	20	4 (20.0)	1.29	0.588	13 (65.0)	3 (15.0)	1 (5.0)	0 (0.0)
6. Vaginal Irritation *	20	4 (20.0)	1.29	0.588	13 (65.0)	3 (15.0)	1 (5.0)	0 (0.0)
7. Urinary Irritation	80	4 (5.0)	1.53	0.757	46 (57.5)	22 (27.5)	6 (7.5)	2 (2.5)
8. Urinary Incontinence	80	0 (0.0)	1.6	0.789	44 (55.0)	27 (33.8)	6 (7.5)	3 (3.8)
9. Lower limb weakness	80	1 (1.3)	1.7	0.806	38 (47.5)	30 (37.5)	8 (10.0)	3 (3.8)
10. Difficulty in walking	80	0 (0.0)	1.85	0.929	34 (42.5)	31 (38.8)	8 (10.0)	7 (8.8)
11. Lower limb numbness	80	0 (0.0)	1.87	0.973	36 (45.0)	25 (31.3)	12 (15)	7 (8.8)
12. Pain/Discharge from wounds	80	1 (1.3)	1.44	0.693	53 (66.3)	17 (21.3)	9 (11.3)	0 (0.0)
14. Problems caring for urostomy	6	0 (0.0)	2.00	0.000	0 (0.0)	6 (100.0)	0 (0.0)	0 (0.0)
15. Embarrassment from urostomy	6	0 (0.0)	1.83	0.983	3 (50.0)	1 (16.7)	2 (33.3)	0 (0.0)
16. Dependent on others for caring for urostomy	6	0 (0.0)	1.33	0.516	4 (66.7)	2 (33.3)	0 (0.0)	0 (0.0)
18. Embarrassment from stoma	40	0 (0.0)	1.70	0.992	23 (57.5)	10 (25.0)	3 (7.5)	4 (10.0)
19. Problems caring for stoma	40	1 (2.5)	1.41	0.715	28 (70.0)	6 (15.0)	5 (12.5)	0 (0.0)
Psychological Impact Scale								
20. Dependence	80	2 (2.5)	1.96	0.918	28 (35.0)	31 (38.8)	13 (16.3)	6 (7.5)
21. Attractiveness	80	2 (2.5)	1.97	0.993	32 (40.0)	23 (28.7)	16 (20.0)	7 (8.8)
Sexual Function Scale								
22. Pain *	80	21 (26.3)	1.44	0.815	42 (52.4)	11 (13.8)	3 (3.8)	3 (3.8)
23. Interest *	80	11 (13.8)	1.84	0.964	32 (40.0)	22 (27.5)	9 (11.3)	6 (7.5)
24. Erectile function *	60	9 (15.0)	2.78	1.205	11 (18.3)	10 (16.7)	9 (15.0)	21 (41.2)
25. Ejaculatory dysfunction *	60	12 (20.0)	2.69	1.274	14 (23.3)	6 (10.0)	9 (15.0)	19 (31.7)

Future Perspective Scale								
26. Results	80	4 (5.0)	2.32	0.883	13 (16.3)	34 (42.5)	21 (26.3)	8 (10.0)
27. Examinations and Tests	80	2 (2.5)	2.36	1.006	17 (21.3)	29 (36.3)	19 (23.8)	13 (16.3)
28. Uncertainty	80	2 (2.5)	2.58	0.947	9 (11.3)	31 (38.8)	22 (27.5)	16 (20.0)
Healthcare Services and Delivery								
29. Information	80	5 (6.3)	3.11	0.847	1 (1.3)	20 (25.0)	24 (30.0)	30 (37.5)
30. Knowledge	80	4 (5.0)	3.5	0.663	0 (0.0)	7 (8.8)	24 (30.0)	45 (56.3)
31. Tests	80	4 (5.0)	3.18	1.016	7 (8.8)	12 (15.0)	17 (21.3)	40 (50.0)
32. Frequency of consultations	80	4 (5.0)	3.18	0.920	4 (5.0)	14 (17.5)	22 (27.5)	36 (45.0)

*These items failed to meet the pre-requisite criteria of <10% missing data at an item level.

Table 8-2 Scalar Level Descriptive Analysis for Hypothesised Scales

Scale	Total No of Items in Scale	Data Completeness (%)	Possible Score Range*	Observed Score Range	Mean Score	SD
Symptoms**	**16**	**100**	**11 - 68**	**12 - 35**	**19.48**	**5.39**
Psychological	**2**	**98.7**	**2 – 8**	**2 – 8**	**3.83**	**1.64**
Sexual Function***	**4**	**65.0**	**4 -16**	**4 - 15**	**6.03**	**4.13**
Future Perspective	**3**	**97.5**	**3 – 12**	**3 - 12**	**7.01**	**2.68**
Healthcare Services	**4**	**95.0**	**4 – 16**	**7 – 16**	**12.28**	**3.91**

***** The possible score range was calculated to reflect the response category of 1 – 4. Missing data were imputed using the half mean imputation. **The minimum score for the symptoms scale is 11 as 5 of the items within this scale are for specific groups i.e. urostomy or stoma, thus leaving 12 items which are applicable to all patients with LRRC. ***Two of the items within the sexual function scale are gender-specific for male patients.

8.3.2 Scale Structure: Multi-trait Analysis on Hypothesised LRRC-QoL Scales

The results for the multi-trait analysis on the hypothesised scales are presented below. The multi-trait, multi-item correlation matrix for the hypothesised scales is presented in Table 8.3 and the item summary statistics are presented in Table 8.4.

Table 8-3 Multi-trait/Multi-item Correlation Matrix for Hypothesised Scales of LRRC-QoL

	Symptom Scale	Psychological Function	Sexual Function	Future Perspective	Healthcare Services
Symptom Scale					
1. Abdominal pain	0.604	0.374	-0.098	0.016	-0.033
2. Back pain	0.619	0.329	-0.135	0.194	0.106
2. Perianal/Buttock Pain	0.676	0.360	0.073	0.126	0.077
4. Rectal Bleeding/ Discharge	0.450	0.204	-0.054	0.003	0.069
5. Vaginal Bleeding/ Discharge	0.196	0.066	-0.465	0.090	0.003
6. Vaginal Irritation	0.207	0.189	-0.505	0.171	-0.068
7. Urinary Irritation	0.315	0.179	0.108	0.061	-0.001
8. Urinary Incontinence	0.598	0.231	-0.193	0.044	-0.020
9. Lower Limb Weakness	0.567	0.231	-0.153	-0.015	0.128
10 Difficulty in walking	0.698	0.347	0.067	0.016	0.068
11. Lower limb numbness	0.378	0.113	0.017	-0.159	0.139
12. Pain/ Discharge from wounds	0.205	-0.016	0.098	-0.116	-0.068
15. Embarrassment from urostomy	0.095	0.081	-0.014	-0.018	0.106
16. Dependent on others for urostomy	0.067	0.026	0.054	-0.076	0.109
18. Embarrassment from stoma	0.097	0.246	-0.055	0.210	0.089
19. Problems caring for	0.152	0.055	-0.053	0.066	0.135

stoma					
Psychological Function					
20. Dependence	0.480	0.817	-0.271	0.355	0.037
21. Attractiveness	0.323	0.844	-0.026	0.504	-0.020
Sexual Function					
22. Pain	-0.082	-0.188	0.546	-0.115	0.193
23. Interest	-0.350	-0.233	0.728	-0.041	0.066
24. Erectile Function	-0.049	-0.028	0.862	0.012	0.106
25. Ejaculatory dysfunction	-0.061	-0.144	0.845	0.013	0.055
Future Perspective					
26. Results	0.026	0.358	0.004	0.857	0.050
27. Examination and Tests	0.031	0.470	-0.049	0.882	0.074
28. Uncertainty	0.204	0.532	-0.026	0.880	0.159
Healthcare Services					
29. Information	0.138	0.033	0.127	0.131	0.861
30. Knowledge	0.041	0.055	0.153	0.177	0.885
31. Tests	0.002	-0.036	0.081	0.047	0.869
32. Frequency of consultations	0.137	-0.011	0.089	0.037	0.892

Table 8-4 Item Summary Statistics for all Hypothesised LRRC-QoL Scales

Scale	No of Items	Mean Item Intercorrelation	Item Discriminant Validity (Range of Scores)	Item to Total Correlations
Symptoms	16	0.170	-0.018 – 0.374	0.018 - 0.552
Psychological Function	2	0.379	-0.026 – 0.504	0.379
Sexual Function	4	0.426	-0.082 – 0.193	0.354 – 0.674
Future Perspective	3	0.644	-0.049 – 0.532	0.686 – 0.727
Healthcare Services	4	0.692	-0.036 – 0.177	0.749 – 0.803

8.3.2.1 Symptom Scale

The hypothesised LRRC-QoL symptom scale consisted of 16 items and 2 skip questions. The rate of missing data at the item level was 1.3 – 15% (Table 8.1). This partly reflects the diversity of items within the scale, with a subset of items specific for women (Items 5-6), patients with a urostomy (Items 15-16) and for patients with a stoma (Items 18-19). Overall the proposed scale structure of the symptoms scale for the LRRC-QoL failed to demonstrate unidimensionality and performed poorly according to the principles of multi-trait scaling analysis. The scale failed to demonstrate good item internal consistency with a poor overall mean item intercorrelation score (Table 8.4). The scale failed to demonstrate equal item-to-total correlations, with 8 of the 16 items failing to meet the pre-requisite criteria of an item-to-total correlation of >0.3. Consequently, these items failed to contribute equally to the total score and therefore do not contribute equal proportions of information to the overall score for the symptoms scale. However, the scale demonstrated good item discriminant validity with item correlations of <0.4 with the scales.

On examining the inter item correlation matrix for the hypothesied symptoms scale (Table

8.5), it becomes apparent that there are clusters of items which correlate highly and demonstrated high item intercorrelations. For example, all items related to pain (LRRC-QoL items 1-3) had item intercorrelations scores of 0.381 – 0.477. Similarly, all items related to gynaecological symptoms (LRRC-QoL items 5-6) had an item intercorrelation score of 0.847. Items related to urinary symptoms (LRRC-QoL items 8-9) had an item intercorrelation of 0.523, items related to lower motor symptoms (LRRC-QoL items 9-11) had an item intercorrelation of 0.357- 0.548, items related to a urostomy (LRRC-QoL items 14-16) had an item intercorrelation of 0.857 – 0.939 and items related to a colorectal stoma (LRRC-QoL items 18-19) had an item intercorrelation of 0.63. This suggests the symptoms scale should be separated out to represent symptoms related to individual biological systems. Further evidence for this is provided by the number of items within the scale which failed to achieve an item intercorrelation value of >0.3, thus suggesting these items did not measure the same underlying construct.

Item	1. Abdo pain	2. Back Pain	3. Perianal or Buttock Pain	4. Rectal Bleeding/ discharge	5.Vaginal Bleeding or discharge	6. Vaginal Irritation	7. Urinary Irritation	8. Urinary Incontinence	9. Lower limb weakness	10. Difficulty in walking	11. Lower limb numbness	12. Pain/ Discharge from wounds	15. Embarrassment from urostomy	16. Dependent on others for caring for urostomy	18. Embarrassment from stoma	19. Problems caring for stoma
1. Abdo pain	1	0.381	0.378	0.288	-0.028	0.143	0.228	0.304	0.194	0.287	0.179	0.011	-0.109	-0.029	0.038	-0.016
2. Back pain	0.381	1	0.477	0.287	0.159	0.178	0.105	0.239	0.309	0.313	0.013	0.056	-0.02	-0.004	0.01	0.055
3. Perianal/ Buttock Pain	0.378	0.477	1	0.492	-0.008	0.093	0.106	0.276	0.148	0.472	0	0.191	0.145	0.165	0.117	0.099
4. Rectal Bleeding/discharge	0.288	0.287	0.492	1	-0.125	-0.086	-0.063	0.218	0.055	0.321	-0.01	0.059	0.368	0.313	-0.057	0.024
5.Vaginal Bleeding or discharge	-0.028	0.159	-0.008	-0.125	1	0.847	-0.248	-0.068	0.087	0.02	-0.016	-0.001	0.13	0.077	0.199	0.177
6. Vaginal Irritation	0.143	0.178	0.093	-0.086	0.847	1	-0.218	-0.048	-0.013	-0.058	-0.046	-0.113	-0.045	-0.073	0.138	0.136
7. Urinary Irritation	0.228	0.105	0.106	-0.063	-0.248	-0.218	1	0.523	0.146	0.175	-0.056	0.038	-0.257	-0.274	-0.086	-0.298
8. Urinary Incontinence	0.304	0.239	0.276	0.218	-0.068	-0.048	0.523	1	0.265	0.331	0.099	0.127	-0.018	-0.119	-0.079	0.015
9. Lower limb weakness	0.194	0.309	0.148	0.055	0.087	-0.013	0.146	0.265	1	0.548	0.454	-0.086	0.016	0.024	-0.092	0.044
10. Difficulty in walking	0.287	0.313	0.472	0.321	0.02	-0.058	0.175	0.331	0.548	1	0.357	-0.017	0.241	0.224	0.017	0.055
11. Lower limb numbness	0.179	0.013	0	-0.01	-0.016	-0.046	-0.056	0.099	0.454	0.357	1	0.023	-0.015	-0.035	0.22	0.359
12. Pain/Discharge	0.011	0.056	0.191	0.059	-0.001	-0.113	0.038	0.127	-0.086	-0.017	0.023	1	0.076	0.076	0.06	0.18

from wounds															
15. Embarrassment from urostomy	-0.109	-0.02	0.145	0.368	0.13	-0.045	-0.257	-0.018	0.016	0.241	-0.015	0.076	1	0.857	0.18	0.164
16. Dependent on others for caring for urostomy	-0.029	-0.004	0.165	0.313	0.077	-0.073	-0.274	-0.119	0.024	0.224	-0.035	0.076	0.857	1	0.095	0.204
18. Embarrassment from stoma	0.038	0.01	0.117	-0.057	0.199	0.138	-0.086	-0.079	-0.092	0.017	0.22	0.06	0.18	0.095	1	0.63
19. Problems caring for stoma	-0.016	0.055	0.099	0.024	0.177	0.136	-0.298	0.015	0.044	0.055	0.359	0.18	0.164	0.204	0.63	1

Table 8-5 Hypothesised Symptoms Scale Item Intercorrelation Matrix

8.3.2.2 Psychological Scale

The hypothesised LRRC-QoL psychological scale consisted of two questions (LRRC-QoL items 20-21). The rate of missing data at item level was 2.5%. The hypothesised psychological scale demonstrated good item internal consistency with a mean item intercorrelation value of 0.379 and equal item-to-total correlations (Table 8.4). The item discriminant validity was good, with higher correlations observed between the items within the hypothesised psychological scale compared to the other scales (Table 8.3). However, there were two correlations of >0.4 between item 21 (physical attraction) and the Future Perspectives scale and between item 20 and the Symptoms scale, thus suggesting a degree of overlap between these concepts.

8.3.2.3 Sexual Function Scale

The hypothesised sexual function scale of the LRRC-QoL consisted of 4 questions, 2 of which were gender-specific for male patients. The rate of missing data at item level for this scale was 13.8-26.3%. Overall, the sexual function scale fulfilled the requirements of multi-trait scaling analysis by demonstrating good item internal consistency, with a mean item intercorrelation value of 0.426 and equal item-to-total correlations (Table 8.4). The hypothesised sexual function scale demonstrated excellent item discriminant validity with low correlations (<0.4) between the items of the sexual function scale and the other hypothesised scales (Table 8.4). However, on inspecting the inter-item correlation matrix for the hypothesised sexual function scale it becomes apparent that not all the items within the scale correlate appropriately (Table 8.6). Item 22 (pain during sexual intercourse) failed to correlate with items 24 and 25 (erectile and ejaculatory function), thus suggesting, these items do not necessarily measure the same underlying construct. Consequently, the hypothesised sexual function scale can be further refined to ensure all the items within the scale have item intercorrelations of >0.3. This can be done by removing item 22, as this item did not correlate

with the other items within the scale. By doing this, it would ensure overall unidimensionality of the scale.

Table 8-6 Item intercorrelation matrix for hypothesises Sexual Function Scale

	22. Pain	23. Interest	24. Erectile function	25. Ejaculatory dysfunction
22. Pain	1	0.573	0.236	0.178
23. Interest	0.573	1	0.422	0.407
24. Erectile function	0.236	0.422	1	0.743
25. Ejaculatory dysfunction	0.178	0.407	0.743	1

8.3.2.4 Future Perspective Scale

The hypothesised future perspective scale of the LRRC-QoL consists of 3 questions (items 26-28). The rate of missing data at item level for this scale was 2.5 – 5%. The hypothesised future perspective scale demonstrated good item internal consistency, with a mean item intercorrelation value of 0.644 (Table 8.7). The scale also demonstrated equal item-to-total correlations (Table 8.4). However, the hypothesised scale failed to fulfill the item discriminant validity criterion for multitrait scaling, with items 27 and 28 also correlating with the psychological scale (Table 8.3). This suggests potential overlap in the measurement of underlying constructs of these items. Consequently, these items will have to be investigated further at exploratory factor analysis to determine whether these items measure the same underlying construct and whether they should be grouped within the same scale.

Table 8-7 Item intercorrelation matrix for hypothesised Future Perspective Scale

	26. Results	27. Examinations and Tests	28. Uncertainty
26. Results	1	0.624	0.632
27. Examinations and Tests	0.624	1	0.676
28. Uncertainty	0.632	0.676	1

8.3.2.5 Healthcare Services

The hypothesised healthcare services scale of the LRRC-QoL consists of 4 questions. The rate of missing data at an item level was 5.0 – 6.3%. The scale demonstrated good item internal consistency, with a mean item intercorrelation value of 0.692 and equal item-to-total correlations (Table 8.4). The inter-item correlation matrix for the hypothesised healthcare services scale is outlined in Table 8.8. The hypothesised healthcare services and delivery demonstrated excellent item discriminant validity, with correlations of <0.40 with all the other hypothesised scales (Table 3).

Table 8-8 Item intercorrelation matrix for hypothesised Healthcare Services Scale

	29. Information	30. Knowledge	31. Tests	32. Frequency of consultations
29. Information	1	0.783	0.61	0.641
30. Knowledge	0.783	1	0.639	0.715
31. Tests	0.61	0.639	1	0.763
32. Frequency of consultations	0.641	0.715	0.763	1

8.3.2.6 Conclusions from Multitrait Scaling on Hypothesised Scales

Multitrait scaling analysis on the hypothesised scales of the LRRC-QoL revealed a number of significant issues in terms of scale unidimensionality amongst the hypothesised scales of LRRC-QoL. The healthcare services scale was the only scale to fulfill all the scaling assumptions of multi-trait analysis and therefore establish scale unidimensionality. Analysis of the symptoms scale revealed poor item intercorrelations and inadequate item-to-total correlations, thus failing to establish the linearity of the underlying scale structure. Similarly, the sexual function scale failed to identify equal item intercorrelations, thus failing to demonstrate uniformity amongst the items of this scale. The psychological function and future perspective scales demonstrated items with poor item discriminant validity, with items within these scales correlating with each other, thus suggesting these items may measure overlapping or similar constructs. Due to the inconsistencies identified in the underlying scale structure of

the hypothesised scales, a pragmatic decision was made to conduct an exploratory factor analysis on all the items of the LRRC-QoL to identify any items which may cluster into scales that were not previously hypothesised.

8.3.3 Scale Structure: Exploratory Factor Analysis

Twenty-nine items were included in the exploratory factor analysis. The KMO measure of sampling adequacy was 0.552 and the Bartlett's statistic was 1246, df=406, $p<0.01$. These statistics supported the suitability of the data for factor analysis despite a sample size of 80. Nine factors emerged with an eigenvalue of 1.00. This was also supported by the scree test criterion (Figure 8.1). These 9 factors accounted for 74.2% of the common variance. Table 8.9 presents the factor loading of the 29 items.

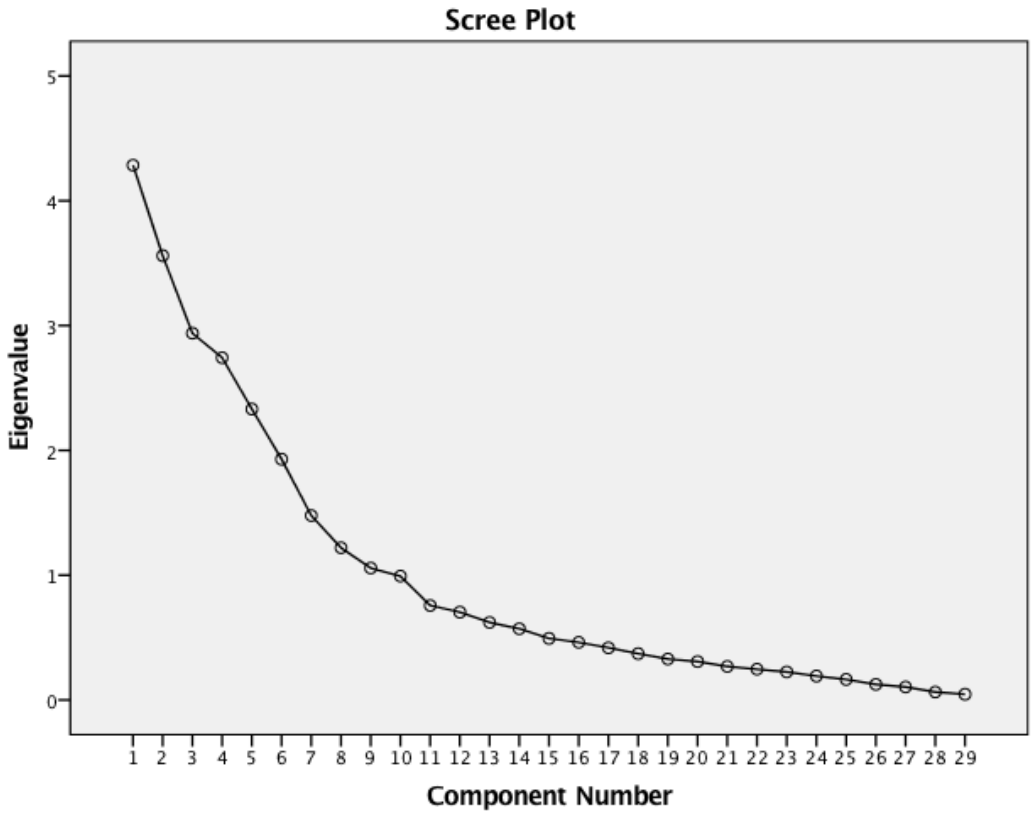


Figure 8-1 Scree plot of extracted number of factors based on Eigenvalue >1.

Table 8-9 Scales derived from Exploratory Factor Analysis

LRRC-QoL Item	Factor								
	1	2	3	4	5	6	7	8	9
30. Knowledge	0.884	0.127	-0.031	0.062	-0.028	-0.015	0.041	0.084	-0.111
32. Frequency of consultations	0.883	-0.039	-0.016	0.013	0.058	0.112	0.1	0.031	0.081
31. Tests	0.862	-0.005	-0.074	-0.059	0.081	0.038	0.044	-0.06	-0.026
29. Information	0.843	0.078	0.041	0.076	0.028	0.048	-0.046	0.154	0.027
28. Uncertainty	0.137	0.858	0.026	0.076	0.046	0.053	0.047	-0.019	0.114
27. Examinations and Tests	0.055	0.847	0.045	0.041	-0.049	-0.121	-0.045	-0.05	-0.071
26. Results	0.023	0.811	0.019	-0.023	-0.05	-0.068	0.021	-0.017	-0.079
21. Attractiveness	-0.093	0.648	0.012	0.229	-0.061	0.073	0.291	0.016	0.195
20. Dependence	0.007	0.422	0.116	0.391	0.193	0.357	-0.161	-0.262	0.154
6. Vaginal Irritation	-0.069	0.15	0.898	0.127	-0.093	0.011	0.094	0.007	-0.161
5.Vaginal Bleeding or discharge	-0.007	0.049	0.89	-0.006	0.079	0.091	0.174	0.029	-0.149
24. Erectile function	0.033	0.091	-0.685	-0.023	0.007	0.19	0.142	0.487	-0.071
25. Ejaculatory dysfunction	-0.017	0.028	-0.67	0.072	0.002	0.105	0.215	0.432	-0.323
3. Perianal/Buttock Pain	0.025	0.118	-0.017	0.792	0.17	0.049	0.152	0.149	0.104
2. Back Pain	0.11	0.157	0.185	0.709	-0.076	0.157	-0.057	-0.023	0.015
1. Abdominal Pain	-0.058	0.013	0.037	0.658	-0.17	0.179	0.029	-0.081	0.172
4. Rectal Bleeding/Discharge	0.066	-0.031	-0.177	0.643	0.424	-0.094	-0.096	-0.224	-0.002
15. Embarrassment from urostomy	0.06	-0.004	0.032	0.007	0.948	0.027	0.105	-0.018	-0.042
16. Dependent on others for caring for urostomy	0.061	-0.067	-0.02	0.055	0.906	0.04	0.088	0.02	-0.141
9. Lower limb weakness	0.102	-0.019	0.034	0.152	-0.006	0.802	-0.109	-0.184	0.122
11. Lower limb numbness	0.115	-0.181	-0.109	0.007	-0.124	0.71	0.366	-0.147	-0.054
10. Difficulty in walking	-0.008	0.044	-0.041	0.393	0.299	0.686	-0.005	0.128	0.216
18. Embarrassment from stoma	0.053	0.26	0.088	-0.069	0.079	0.023	0.823	-0.069	-0.008
19. Problems caring for stoma	0.131	0.018	0.074	0.01	0.111	0.116	0.8	-0.137	-0.151
12. Pain/Discharge from wounds	-0.092	-0.207	-0.13	0.266	0.037	-0.275	0.44	0.052	0.146
22. Pain during sexual intercourse	0.196	-0.141	0.014	0.089	0.027	-0.208	-0.162	0.79	0.096
23. Interest in sex	0.048	-0.012	-0.333	-0.215	-0.054	-0.13	-0.141	0.719	-0.048
7. Urinary Irritation	-0.009	0.099	-0.159	0.05	-0.224	0.071	-0.11	0.177	0.83
8. Urinary Incontinence	-0.012	0	0.012	0.267	0.005	0.132	0.017	-0.153	0.792

The nine emerging factors were renamed as the following:

Factor 1 – Healthcare Services

Factor 2 – Psychological Impact

Factor 3 – Sexual Function * This is a gender specific factor – with two items specific to each gender.

Factor 4- Pain and discomfort

Factor 5 – Urostomy Related Symptoms

Factor 6 – Lower limb symptoms

Factor 7 – Stoma and wound related issues

Factor 8 – Sexual Interest

Factor 9 – Urinary Symptoms

8.3.4 Scale Structure: Multitrait Scaling on Revised Scales

Following the exploratory factor analysis eight new scales were identified. The only original scale to be retained was the Healthcare Services scale. Subsequently, further analyses were conducted on the 8 new scales using the principles of multi-trait scaling analysis. The multi-trait, multi-item correlation matrix for the revised scales is presented in Table 8.10 and the item summary statistics are presented in Table 8.11.

Table 8-10 Multi-trait/Multi-item Correlation Matrix for Revised Scales of LRRC-QoL

	Healthcare Services	Psychological Impact	Sexual Function	Pain and Discomfort	Urostomy	Lower Limb Symptoms	Stoma and Wound	Sexual Interest	Urinary Symptoms
Healthcare Services									
29. Information	0.861	0.107	0.106	0.105	0.098	0.125	-0.006	0.153	0.043
30. Knowledge	0.885	0.148	0.113	0.073	0.040	0.056	0.101	0.168	-0.084
31. Tests	0.869	0.017	0.035	0.03	0.135	0.102	0.078	0.079	-0.053
32. Frequency of consultations	0.892	0.021	0.05	0.081	0.107	0.202	0.123	0.103	0.047
Psychological Impact									
26. Results	0.050	0.759	0.109	0.038	-0.083	-0.096	0.082	-0.066	0.011
27. Examinations and Tests	0.074	0.825	0.022	0.087	-0.050	-0.130	0.054	-0.063	-0.010
28. Uncertainty	0.159	0.850	0.065	0.198	0.018	0.044	0.137	-0.093	0.160
20. Dependence	0.037	0.603	-0.178	0.437	0.159	0.377	-0.026	-0.280	0.202
21. Attractiveness	-0.020	0.720	0.087	0.281	-0.049	0.110	0.271	-0.123	0.188
Sexual Function									
5.Vaginal Bleeding or discharge	0.004	0.092	0.844	0.060	0.095	0.024	0.163	-0.270	-0.183
6. Vaginal Irritation	-0.068	0.203	0.844	0.178	-0.065	-0.063	0.067	-0.252	-0.154
24. Erectile function	0.106	-0.003	0.739	-0.031	0.022	0.125	0.076	0.377	0.049
25. Ejaculatory dysfunction	0.054	-0.053	0.739	0.010	0.070	0.089	0.157	0.337	-0.158
Pain and Discomfort									
1. Abdominal Pain	-0.033	0.173	-0.033	0.658	-0.079	0.277	0.018	-0.137	0.304

2. Back Pain	0.106	0.279	-0.042	0.743	-0.014	0.257	0.049	-0.133	0.196
3. Perianal/Buttock Pain	0.077	0.244	0.150	0.825	0.159	0.259	0.175	-0.027	0.218
4. Rectal Bleeding/Discharge	0.069	0.090	-0.057	0.702	0.358	0.154	0.000	-0.109	0.086
Urostomy									
15. Embarrassment from urostomy	0.106	0.022	0.035	0.139	0.976	0.103	0.197	-0.053	-0.159
16. Dependent on others for caring for urostomy	0.109	-0.042	0.113	0.157	0.949	0.090	0.168	-0.041	-0.226
Lower Limb Symptoms									
9. Lower limb weakness	0.128	0.089	-0.029	0.24	0.020	0.819	-0.061	-0.280	0.235
10. Difficulty in walking	0.068	0.161	0.148	0.048	0.243	0.797	0.027	-0.077	0.289
11. Lower limb numbness	0.139	-0.063	0.141	0.052	-0.024	0.774	0.286	-0.19	0.023
Stoma and Wound									
12. Pain/Discharge from wounds	-0.068	-0.089	0.127	0.116	0.079	-0.03	0.465	-0.001	0.094
18. Embarrassment from stoma	0.089	0.255	0.133	0.041	0.15	0.071	0.846	-0.208	-0.094
19. Problems caring for stoma	0.135	0.070	0.119	0.062	0.187	0.202	0.847	-0.192	-0.164
Sexual Interest									
22. Pain	0.193	-0.162	0.21	0.04	-0.003	-0.198	-0.174	0.868	0.055
23. Interest	0.066	-0.130	0.353	-0.253	-0.08	-0.201	-0.179	0.904	-0.061
Urinary Symptoms									
7. Urinary Irritation	-0.001	0.12	-0.018	0.122	-0.273	0.105	-0.164	0.117	0.876
8. Urinary Incontinence	-0.02	0.131	-0.234	0.349	-0.061	0.287	0.008	-0.134	0.869

Table 8-11 Item Summary Statistics for all Revised LRRC-QoL Scales

Scale	No of Items	Mean Item Intercorrelation	Item Discriminant Validity (Range of Scores)	Item to Total Correlations
Healthcare Services	4	0.692	-0.006 – 0.148	0.749 – 0.803
Psychological Impact	5	0.456	-0.083 – 0.437	0.404 – 0.743
Sexual Function				
Female	2	0.844	-0.068 – 0.178	0.847
Male	2	0.739	-0.156 – 0.378	0.743
Pain and Discomfort	4	0.384	-0.137 – 0.279	0.447 – 0.613
Urostomy Related Symptoms	2	0.857	-0.226 – 0.197	0.857
Lower Limb Symptoms	3	0.453	-0.280 – 0.289	0.458 – 0.607
Stoma and Wound Related Issues	3	0.290	-0.208 – 0.255	0.125 – 0.611
Sexual Interest	2	0.573	-0.253 – 0.193	0.573
Urinary Symptoms	2	0.523	-0.234 – 0.349	0.523

8.3.4.1 Healthcare Services

The healthcare services scale was unchanged from its initial hypothesised version, therefore all its original values for item intercorrelations and item-to-total correlations remain the same. The scale retains its item discriminant validity, with correlations of <0.4 with the other scales of the revised LRRC-QoL (Table 8.10).

8.3.4.2 Psychological Impact

The revised psychological impact scale consisted of 5 questions. The scale demonstrated good internal item consistency with a mean item intercorrelation value of 0.456 (Table 8.11). On

examining the item correlation matrix for the scale, item 20 (dependence) was found to have a low item intercorrelation value with item 26 (anxiety regarding results) (Table 8.12). Item 20 regarding dependence was the only item within the psychological impact scale which did not demonstrate good item discriminate validity, as it correlated with the Pain and Discomfort scale (Table 8.10). All the other items within the scale displayed excellent correlations with the Psychological Impact scale and low correlations with the other scales. Item 20 had a lower item-to-total correlation score than the other items within the scale. All the other items within the scale had similar item-to-total correlations. As item 20 was consistently being highlighted as a problematic item within this scale, a pragmatic decision was made to remove this item from the scale.

Table 8-12 Item intercorrelation matrix for new Psychological Impact Scale

	26. Results	27. Examinations and Tests	28. Uncertainty	20. Dependence	21. Attractiveness
26. Results	1	0.624	0.632	0.217	0.372
27. Examinations and Tests	0.624	1	0.676	0.301	0.474
28. Uncertainty	0.632	0.676	1	0.410	0.472
20. Dependence	0.217	0.301	0.410	1	0.379
21. Attractiveness	0.372	0.474	0.472	0.379	1

8.3.4.3 Sexual Function

The new sexual function scale consisted of 4 questions, which were gender specific. This scale was analysed individually for each gender. The mean item intercorrelation for the female sexual function scale was 0.844 and for the male sexual health was 0.739 (Table 8.11). The item discriminant validity overall was good for the scale (Table 8.10). The item-to-total correlations for all the items included in the scale exceeded 0.3 (Table 8.11).

8.3.4.4 Sexual Interest

The revised sexual interest scale consisted of two questions. The scale demonstrated good item internal consistency with a mean item intercorrelation of 0.573 and equal item to total correlations (Table 8.11). The scale demonstrated good item discriminant validity with low correlations with the other scales (Table 8.10).

8.3.4.5 Pain and Discomfort

The new Pain and Discomfort scale consisted of 4 questions. The mean item intercorrelation was 0.384 (Table 8.11). On reviewing the item intercorrelation matrix for this scale item 4 (rectal bleeding and discharge) had item intercorrelations of <0.3 with items 1 and 2 (abdominal pain and back pain) (Table 8.13). Subsequently, an executive decision was made to remove the item from the scale and retain it as an individual item. Upon removing this item the mean item intercorrelation was 0.421, with item intercorrelations of >0.3 for all the remaining items within the scale. This scale was subsequently renamed as the pain scale.

Table 8-13 Item intercorrelation matrix for new Pain and Discomfort Scale

	1. Abdominal Pain	2. Back Pain	3. Perianal/ Buttock Pain	4. Rectal Bleeding/ Discharge
1. Abdominal Pain	1	0.381	0.378	0.288
2. Back Pain	0.381	1	0.477	0.287
3. Perianal/Buttock Pain	0.378	0.477	1	0.492
4. Rectal Bleeding/Discharge	0.288	0.287	0.492	1

8.3.4.6 Urostomy Related Symptoms

The new Urostomy Related Symptoms scale consisted of 2 items. The scale fulfilled all the pre-requisite criteria of multi-trait scaling, with good item internal consistency with a mean item intercorrelation of 0.857 and equal item-to-total correlations (Table 8.11). Excellent item

discriminant validity was displayed with low correlations between the items of the urostomy related symptoms and the other scales within the LRRC-QoL (Table 8.10). However, the results for this scale must be interpreted with caution as only a total of 6 patients answered the items relevant to a urostomy.

8.3.4.7 Lower Limb Symptoms

The new Lower Limb Symptoms scale consisted of 3 items. The mean item intercorrelation was good at 0.453 (Table 8.11). The item intercorrelation matrix for the lower limb symptoms is presented in Table 8.14. The scale demonstrated good item discriminant validity (Table 8.10). The scale demonstrated equal item-to-total correlations (Table 8.11).

Table 8-14 Item intercorrelation matrix for new Lower Limb Scale

	9. Lower limb weakness	10. Difficulty in walking	11. Lower limb numbness
9. Lower limb weakness	1	0.548	0.454
10. Difficulty in walking	0.548	1	0.357
11. Lower limb numbness	0.454	0.357	1

8.3.4.8 Stoma and Wound Related Issues

The new stoma and wound related issues scale consisted of 3 items. The scale demonstrated poor item internal consistency with a mean item intercorrelation of 0.29 (Table 8.11). On examining the item intercorrelation matrix for this scale, item 12 (wound related pain and discharge) was identified as a problematic item (Table 8.15). Items 18 and 19 (embarrassment from stoma and problems caring for stoma) had good inter-item correlations of 0.63 (Table 8.15). However, both items failed to correlate with item 12. Item 12 demonstrated a lower item-to-total correlation when compared to the other two items within the scale. Thus, suggesting non-linearity in the contribution of all the items to the overall scale score.

Consequently, a pragmatic decision was made to remove item 12 from the scale and retain this as an individual item within the framework of the LRRC-QoL. On removing item 12 the mean inter-item correlation was 0.788 and the item-to-total correlation was 0.630. Subsequently, this scale was renamed as the Stoma scale.

Table 8-15 Inter-item correlation matrix for new Stoma and Wound Scale

	12. Pain/Discharge from wounds	18. Embarrassment from stoma	19. Problems caring for stoma
12. Pain/Discharge from wounds	1	0.06	0.18
18. Embarrassment from stoma	0.06	1	0.63
19. Problems caring for stoma	0.18	0.63	1

8.3.4.9 Urinary Symptoms

The new urinary symptoms scale consisted of two items. The scale demonstrated good internal item consistency with a mean item intercorrelation was 0.523 and equal item to total correlations (Table 8.11). The item discriminant validity of the scale was excellent.

8.3.5 LRRC-QoL Finalised Scale Structure

Based on the combined results of the multitrait scaling analysis and the factor analysis the final scale structure of the LRRC-QoL was determined. The final scale structure consists of 28 items organised into 9 scales and 2 individual items. The 9 scales were healthcare services, psychological impact, sexual function, pain, urostomy related symptoms, lower limb symptoms, sexual interest and urinary symptoms. Descriptive analyses for the finalised LRRC-QoL scales are presented in Table 8.16. The total computable score range for the finalised scales of the LRRC-QoL was 86.2 – 100%.

Table 8-16 Descriptive Analysis for Finalised LRRC-QoL Structure

Scale	Total No of Items in Scale	Data Completeness (%)	Possible Score Range*	Observed Score Range	Mean Score	SD
Healthcare Services	4	95.0	4 – 16	7 – 16	12.28	3.91
Psychological Impact	5	97.5	5 – 20	5 - 20	11.15	3.56
Sexual Function **						
Female	2	80.0	2 - 8	2 - 5	2.62	1.02
Male	2	86.7	2 – 8	2 - 8	4.60	3.02
Pain	3	100	3 - 12	3 - 12	5.43	2.01
Urostomy	2	100	2 – 8	2 – 5	3.16	1.16
Lower Limb	3	100	2 - 12	2 - 12	5.41	2.14
Stoma	2	98.7	2 – 8	2 – 8	3.07	1.26
Sexual Interest	2	66.2	2 – 8	2 – 8	2.65	1.81
Urinary Symptoms	2	95.0	2 – 8	2 – 8	3.15	1.34
Item						
Rectal Bleeding/Discharge	1	98.8	1- 4	1 – 4	1.55	0.81
Wound Pain/Discharge	1	98.8	1-4	1 – 3	1.44	0.69

*The possible score range was calculated to reflect the response category of 1-4. ** This is a gender-specific scale and therefore only contains 2 items per gender.

8.3.6 Scale Reliability

Scale reliability of the LRRC-QoL was established using two different measures of reliability; including Cronbach's Alpha to assess scale reliability and the intra-class correlation (ICC) using the test-retest method to assess temporal stability at a scalar level. The results of the reliability tests are outlined in Table 8.17. Overall, the LRRC-QoL demonstrated good reliability across both scores. Cronbach's Alpha values of >0.70 were fulfilled by the majority of the scales, except the pain and urinary symptoms scales. Temporal stability, using the test-retest measure, of the LRRC-QoL is good, with ICC values of >0.7. However, the

values obtained for both Cronbach's Alpha and the ICC should be interpreted with caution as the majority of the values are associated with wide confidence intervals, thus suggesting the sample size is not sufficient to confirm the reliability of the LRRC-QoL. Therefore, the reliability of the LRRC-QoL will need to be confirmed within a larger sample.

Table 8-17 Reliability scores of the LRRC-QoL

Scale	**Cronbach's Alpha** (95% Confidence Intervals)	**ICC** (95% Confidence Intervals)
Healthcare Services	0.89 (0.84 – 0.92)	0.70 (0.53 – 0.81)
Psychological Impact	0.80 (0.70 – 0.85)	0.76 (0.62 – 0.85)
Sexual Function Male Female	 0.85 (0.76 – 0.90) 0.91 (0.87 – 0.94)	 0.74 (0.62 – 0.82) 0.85 (0.77 – 0.89)
Pain	0.67 (0.52 – 0.78)	0.75 (0.57 – 0.85)
Urostomy Related Symptoms	0.89 (0.82 – 0.92)	0.96 (0.94 – 0.97)
Lower Limb Symptoms	0.70 (0.57 – 0.80)	0.82 (0.71 – 0.89)
Stoma	0.76 (0.62 – 0.84)	0.85 (0.76 – 0.91)
Sexual Interest	0.72 (0.56 – 0.82)	0.91 (0.85 – 0.94)
Urinary Symptoms	0.68 (0.51 – 0.79)	0.71 (0.56 – 0.82)

8.3.7 Scale Validity

8.3.7.1 Construct Validity

Construct validity of the LRRC-QoL can be assumed as the second round of multi-trait scaling analysis has produced 9 scales which measure the same underlying construct. The majority of the scales fulfilled the pre-requisite criteria of multi-trait scaling to establish unidimensionality and consequently, construct validity of each individual scale.

8.3.7.2 Convergent Validity

Following the determination of the new scale structure of the LRRC-QoL based on the factor analysis and multi-trait scaling analysis a number of *a priori hypotheses* were made regarding convergent validity of the LRRC-QoL with the EORTC CR29 and FACT-C.

The following hypotheses were made:

- The LRRC-QoL psychological impact scale would correlate (r >0.45) with the EORTC CR29 body image scale and the FACT-C emotional well being scale.
- The LRRC-QoL pain scale would correlate (r>0.45) with the FACT-C physical well being scale.
- The LRRC-QoL stoma scale would correlate (r>0.45) with the EORTC frequency of defaecation scale.
- The LRRC-QoL urinary symptoms scale would correlate (r>0.45) with the EORTC urinary frequency scale.
- Lower correlations (<0.45) were hypothesised between the remaining LRRC-QoL, EORTC CR29 and FACT-C scales.

The convergent validity of the LRRC-QoL and its scales were evaluated through correlational analyses using the Pearson's product moment correlation (r) with the scales of the EORTC QLQ CR-29 and FACT-C questionnaires. Table 8.18 and 8.19 summarise the Pearson product moment correlations across the LRRC-QoL subscales and the EORTC CR29 and FACT-C scales respectively. Overall, positive correlations were moderate to high (r >0.45) in the hypothesised direction. As expected significant positive correlations were identified between the LRRC-QoL stoma scale and the EORTC frequency of defaecation scale, the LRRC-QoL pain scale and the FACT-C physical well-being scale and the LRRC-QoL psychological impact scale and the FACT-C emotional well-being scale. These identified correlations are statistically significant and underlie the same underlying measured themes, thus supporting

convergent validity. The hypothesised correlation between the LRRC-QoL urinary symptoms scale and with the EORTC urinary frequency scale was the only hypothesised correlation which failed to correlate, with a r value of -0.11, p=0.33.

A number of interesting correlation patterns emerged between the LRRC-QoL and the EORTC CR29 and the FACT-C which were not hypothesised. Positive correlations between the LRRC-QoL pain scale and the EORTC CR29 blood and mucus in stool, the LRRC-QoL stoma scale and the EORTC CR29 urinary frequency scale and the EORTC body image scale, the LRRC-QoL lower limb symptoms scale and the FACT-C physical well being scale and the LRRC-QoL stoma and scale and the FACT-C physical well being scale were also revealed. This suggests there may be inconsistencies in the convergent validity for the LRRC-QoL.

8.3.7.3 Known-Groups Comparison

A number of *a priori hypotheses* were made with regards to the known-groups comparison. It was hypothesised that the LRRC-QoL would be able to discriminate scores between clinically significant groups, including gender, presence of concurrent metastatic disease, recurrent disease location (central, anterior, lateral or posterior), treatment intention (curative versus palliative), pre-operative treatments (pre-operative treatment i.e. chemoradiation/radiotherapy/chemotherapy versus none), palliative treatments (chemoradiation, chemotherapy or surgery) and current disease status (recurrence versus recurrence and metastatic disease. Due to the small number of patients who were included in the LRRC-QoL with a urostomy (n=6), a pragmatic decision was made not to include the Urostomy-Related Symptoms scale in the known-groups comparison as it is unlikely to yield any meaningful results. Similarly, a pragmatic decision was made not to conduct any analyses for the palliative treatments group, due to the small number of patients undergoing palliative chemoradiation (n=4) and surgery (n=1). With regards to the current disease status clinical category a decision was made to combine the locally re-recurrent disease group and distant

disease recurrence group as a disease recurrence group and compare this to the disease-free group. The comparisons between LRRC-QoL scores and different clinical groups are outlined in Table 8.20 and 8.21.

The LRRC-QoL was able to discriminate between some clinically relevant groups. The sexual interest scale was able to demonstrate significant differences amongst men and women. The sexual function scale was able to demonstrate differences in obtained scores between patients treated with curative intent versus palliative intent. The stoma scale was able to detect statistically significant differences between patients undergoing treatment with a curative intent compared to palliative intent.

A number of clinically relevant trends emerged, which failed to fulfil statistical criteria between LRRC-QoL scores and clinical categories. The psychological impact scale revealed a trend towards higher LRRC-QoL scores in women and in patients with centrally and posteriorly located recurrent disease. The sexual function scale revealed a trend towards higher scores in patients undergoing no pre-operative treatment compared to those undergoing pre-operative treatment. The lower limb symptoms scale revealed a trend towards higher scores in centrally and anteriorly located recurrent disease and in patients with disease recurrence.

Table 8-18 Convergent validity between LRRC-QoL scales and EORTC CR29 scales

LRRC-QoL Scale	EORTC Scale											
	Urinary Frequency			Blood/Mucus in Stool			Frequency of defaecation			Body Image		
	r	P Value	95% CI	r	P Value	95% CI	r	P Value	95% CI	r	P Value	95% CI
Healthcare Services	0.205	0.07	-0.026 – 0.398	0.128	0.26	-0.085 - 0.341	0.078	0.50	-0.106 – 0.291	0.071	0.53	-0.124 – 0.272
Psychological Impact	0.122	0.29	0.067 – 0.299	0.199	0.08	0.001 – 0.395	0.105	0.362	-0.076 – 0.365	0.481	0.01	0.270 -0.646
Sexual Function	0.177	0.12	-0.070 - 0.418	0.118	0.30	-0.125 - 0.344	0.203	0.07	-0.052 – 0.440	0.315	0.005	0.063 – 0.522
Pain	0.271	0.01	0.040 – 0.453	0.449	0.001	0.198 – 0.614	0.034	0.77	-0.199 - 0.235	0.364	0.01	0.141 – 0.541
Urostomy Related Symptoms	0.317	0.01	0.124 – 0.473	0.042	0.716	-0.136 – 0.160	0.243	0.03	0.011 – 0.408	0.101	0.38	-0.004 – 0.201
Lower Limb Symptoms	0.320	0.01	0.096 – 0.486	0.204	0.075	-0.022 - 0.41	0.086	0.45	-0.153 – 0.280	0.212	0.06	0.011 – 0.394
Stoma	0.509	0.01	0.365 – 0.645	0.308	0.01	0.076 – 0.518	0.841	0.01	0.788 – 0.891	0.458	0.01	0.242 – 0.642
Sexual Interest	-0.204	0.07	-0.414 – 0.036	-0.123	0.28	-0.352 - .128	-0.256	0.02	-0.435 - -0.044	-0.185	0.10	-0.388 – 0.027
Urinary Symptoms	-0.088	0.44	-0.376 – 0.178	-0.115	0.31	-0.406 – 0.115	-0.195	0.09	-0.366 – 0.013	-0.175	0.12	-0.410 - 0.052

r = Pearson’s product moment correlation coefficient

Table 8-19 Convergent validity between LRRC-QoL scales and FACT-C scales

LRRC-QoL Scale	FACT-C Scale														
	Physical Well-Being			Social Well Being			Emotional Well Being			Functional Well Being			Colorectal Scale		
	r	P Value	95% CI	r	P Value	95% CI	r	P Value	95% CI	r	P Value	95% CI	r	P Value	95% CI
Healthcare Services	0.157	0.19	-0.081 – 0.332	0.062	0.61	-0.170 – 0.327	-0.012	0.92	-0.223 – 0.180	0.012	0.92	-0.230 – 0.304	0.069	0.56	-0.170 – 0.327
Psychological Impact	0.266	0.02	0.014 - 0.473	0.027	0.82	-0.193 – 0.237	0.476	0.001	0.246 – 0.655	0.098	0.41	-0.15 -0.328	0.152	0.21	-0.073 – 0.352
Sexual Function	0.140	0.24	-0.121- 0.402	0.184	0.12	-0.066 – 0.415	0.192	0.112	-0.053 - 0.423	0.257	0.03	0.018 – 0.480	0.235	0.05	-0.009 – 0.459
Pain	0.495	0.001	0.232 – 0.696	0.005	0.97	-0.215 – 0.218	0.268	0.01	0.029 – 0.479	-0.196	0.10	-0.388 – 0.007	0.017	0.89	-0.199 – 0.231
Urostomy Related Symptoms	0.240	0.04	0.079 – 0.401	0.137	0.25	0.027 – 0.258	0.199	0.09	0.002 - 0.363	0.076	0.53	-0.077 – 0.275	0.143	0.23	-0.019 – 0.336
Lower Limb Symptoms	0.417	0.001	0.193 – 0.613	0.163	0.17	-0.050 – 0.352	0.142	0.24	-0.147 – 0.290	-0.039	0.74	-0.262 - 0.169	0.089	0.47	-0.147 - 0.290
Stoma	0.395	0.001	0.166 – 0.589	0.342	0.01	0.163 – 0.537	0.363	0.01	0.135 – 0.578	0.360	0.01	0.189 – 0.557	0.415	0.01	0.250 – 0.566
Sexual Interest	-0.316	0.01	-0.494 - -0.108	-0.156	0.19	-0.41 – 0.086	-0.177	0.14	-0.41 – 0.086	-0.061	0.61	-0.315 – 0.171	-0.115	0.34	-0.375 – 0.138
Urinary Symptoms	-0.088	0.46	-0.344 - 0.147	-0.346	0.003	-0.581 - -0.104	-0.211	0.08	-0.439 – 0.019	-0.366	0.002	-0.583 - -0.109	-0.371	0.002	-0.555 - -0.159

r = Pearson's product moment correlation coefficient

Table 8-20 Known Groups Comparison for LRRC-QoL

Scale	Healthcare Services				Psychological Impact				Sexual Function				Pain and Discomfort			
Groups	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**
Gender																
Male	60	12.47	3.64	0.48	60	10.40	3.74	0.06	60	-	-	-	60	5.23	1.97	0.30
Female	20	11.75	4.70		20	12.20	3.81		20	-	-		20	5.78	2.22	
Presence of Concurrent Metastatic Disease																
No	46	12.22	4.25	0.93	46	10.87	3.64	0.64	46	3.72	2.82	0.43	46	5.33	2.04	0.99
Yes	11	12.09	4.57		11	11.45	4.16		11	3.00	2.19		11	5.30	2.11	
Recurrent Disease Location																
Central	22	12.77	4.57		22	10.95	3.84		22	3.73	2.68		22	5.86	2.60	
Anterior	5	13.20	2.77	0.71	5	9.20	2.28	0.07	5	5.00	2.24		5	5.20	1.64	0.28
Lateral	19	11.53	3.82		19	10.11	3.45		19	3.11	2.77	0.55	19	4.61	1.33	
Posterior	12	11.58	4.94		12	13.25	3.55		12	3.33	2.84		12	5.41	1.62	
Treatment Intent																
Curative	37	12.43	4.45	0.49	37	11.27	3.11	0.46	37	4.22	2.94	0.01	37	5.40	2.03	0.65
Palliative	21	11.67	3.90		21	10.52	4.58		21	2.38	1.69		21	5.15	2.03	
Pre-operative Treatments																
None	9	11.89	4.83	0.60	9	11.56	3.28	0.99	9	6.00	3.16	0.08	9	5.22	2.33	0.72
Pre-operative Treatment	22	12.86	3.90		22	11.54	2.92		22	4.00	2.70		22	5.54	2.10	
Current Disease Status																
Disease Free	22	11.36	5.23	0.31	22	11.32	3.41	0.43	22	4.59	2.77	0.09	22	4.86	1.83	0.11
Disease Recurrence	15	12.86	2.77		15	12.26	3.65		15	3.00	2.67		15	5.86	1.84	

Table 8-21 Known Groups Comparison for LRRC-QoL

Scale	Lower Limb Symptoms				Stoma				Sexual Interest				Urinary Symptoms			
Groups	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**	**N**	**Mean**	**SD**	**P Value**
Gender																
Male	60	5.38	2.27	0.90	60	2.9	1.86	0.44	60	2.91	1.81	0.01	60	3.1	1.50	0.50
Female	20	5.45	1.87		20	3.3	2.38		20	1.85	1.63		20	2.9	1.02	
Presence of Concurrent Metastatic Disease																
No	46	5.32	2.04	0.41	46	3.15	2.01	0.15	46	2.56	1.64	0.90	46	3.47	1.53	0.24
Yes	11	5.90	2.34		11	2.18	1.99		11	2.63	2.50		11	2.90	1.04	
Recurrent Disease Location																
Central	22	6	2.50		22	2.81	2.17		22	3	1.90		22	3.81	1.65	
Anterior	5	7.2	2.38		5	2.4	1.34		5	1.8	1.30		5	3.2	1.10	
Lateral	19	4.94	1.61	0.06	19	3	1.94	0.87	19	2.05	1.68	0.29	19	2.68	0.75	0.06
Posterior	12	4.75	1.48		12	3.25	2.26		12	2.75	2.01		12	3.66	1.72	
Treatment Intent																
Curative	37	5.72	2.46	0.27	37	3.40	2.00	0.01	37	2.70	1.63	0.39	37	3.40	1.24	0.76
Palliative	21	5.09	1.30		21	2.09	1.81		21	2.23	2.14		21	3.28	1.79	
Pre-operative Treatments																
None	9	5.22	2.94	0.74	9	3.55	1.33	0.64	9	2.44	1.94	0.74	9	3.11	1.05	0.72
Pre-operative treatment	22	5.59	2.44		22	3.95	2.10		22	2.68	1.46		22	3.27	1.27	
Current Disease Status																
Disease Free	22	5.09	2.07	0.09	22	3.41	2.20	0.69	22	3.00	1.60	0.08	22	3.36	1.22	0.56
Disease Recurrence	15	6.33	2.22		15	3.13	2.03		15	2.00	1.73		15	3.66	1.71	

8.3.8 Sample Size Justification

This study reports the results of an interim analysis conducted on British patients completing the LRRC-QoL. To mitigate the effects of having a smaller sample size and to examine whether the obtained results were justified and valid a number of key aspects of the analysis were further examined including key components of the exploratory factor analysis and confidence intervals for Cronbach's Alpha, Intraclass Correlation and Pearsons product moment correlation coefficient.

The communality of variables, degree of overdetermination and size of the factor loadings were examined for the LRRC-QoL to ensure that the scale structure had been appropriately determined by exploratory factor analysis. The communalities of the individual items are outlined in Table 8.22. Only two items (item 1 and 12) failed to meet the baseline criterion of an item communality value of >0.6. However, the mean overall item communality value was 0.74, which meets the minimum criteria of a mean overall value of >0.70.

The extracted factors are outlined in Table 8.9. The factors extracted by the exploratory factor analysis were highly overdetermined with 4 of the 9 factors (healthcare services, sexual function, pain and discomfort, lower limb symptoms) consisting of more than 3 variables with high factor loadings. Three factors consisted of two variables (urostomy-related symptoms, sexual interest and urinary symptoms) however these variables had high factor loadings >0.7. Two of the nine factors extracted (psychological function and stoma and wound related issues) consisted of one variable with a lower factor loading. Both of the variables in these factors (items 20 and items 12) were noted to be problematic at subsequent multitrait scaling analysis and were appropriately removed. Overall, the factor loadings of the variables onto the factors were high for the majority with few crossloadings of variables. Based on the overall communality of the variables, the degree of overdetermination and the

size of the factor loadings, the sample size employed in this analysis was adequate to determine the scale structure of the LRRC-QoL using the principles of exploratory factor analysis.

Table 8-22 Communalities of LRRC-QoL Items

Item	Communalities
1. Abdominal Pain	0.536
2. Back Pain	0.608
3. Perianal/Buttock Pain	0.73
4. Rectal Bleeding/Discharge	0.698
5.Vaginal Bleeding or discharge	0.863
6. Vaginal Irritation	0.893
7. Urinary Irritation	0.825
8. Urinary Incontinence	0.739
9. Lower limb weakness	0.74
10. Difficulty in walking	0.78
11. Lower limb numbness	0.736
12. Pain/Discharge from wounds	0.433
15. Embarrassment from urostomy	0.918
16. Dependent on others for caring for urostomy	0.862
18. Embarrassment from stoma	0.772
19. Problems caring for stoma	0.731
20. Dependence	0.627
21. Attractiveness	0.614
22. Pain	0.77
23. Interest	0.718
24. Erectile function	0.777
25. Ejaculatory dysfunction	0.803
26. Results	0.673
27. Examinations and Tests	0.751
28. Uncertainty	0.782
29. Information	0.753
30. Knowledge	0.824
31. Tests	0.767
32. Frequency of consultations	0.815

The reliability scores of the LRRC-QoL using Cronbach's Alpha and Intraclass correlation and the associated confidence intervals are outlined in Table 17. For the Cronbach's Alpha values the confidence intervals for the majority of the scales were wide. The confidence intervals for the Cronbach's alpha values for the pain, stoma, lower limb symptoms, sexual interest and urinary

symptoms scales were wider than for the other scales. For the IntraClass correlation values the majority of the confidence values were of acceptable widths. The confidence intervals for the healthcare services, pain and urinary symptoms scales are wider than for the other scales. The scores for the Pearson's product moment correlation values for the convergent validity are highlighted in Table 18 and 19. Overall, the confidence intervals are wide for the majority of the obtained values. Based on the size of the confidence intervals for reliability, the sample size of the LRRC-QoL is adequate. However, this is not applicable when assessing validity using Pearson's product moment correlation coefficient. The width of the confidence intervals seen for the Pearson's correlation coefficients are too wide for any meaningful interpretation of the obtained value, thus suggesting the sample study is underpowered and inadequate. Therefore, both the reliability and validity of the LRRC-QoL will have to be re-assessed in a larger sample size.

8.4 Discussion

Phase III of the LRRC-QoL project adapts and validates the measure for use in British patients with LRRC in a step-wise and methodical fashion. The hypothesised scales of the LRRC-QoL failed to fulfil the principles of multitrait analysis during the first round of testing, with significant issues identified in four out of the five hypothesised scales. Subsequently, exploratory factor analysis was employed to identify the scale structure of the LRRC-QoL, this identified 9 scales, which performed well on subsequent multitrait scaling analysis. The final version of the LRRC-QoL for use in the UK consists of 28 items and 2 skip questions organised into 9 scales and 2 individual item.

Employing a pre-specified, multi-step process ensured we developed a questionnaire which was reliable and valid in this group of patients. The first step of data analysis ensured a well-balanced questionnaire was created with no ceiling or floor effects. This led to the removal of Item 14 (problems regarding the care of a urostomy) during the initial analysis phase. Using the principles of

multitrait scaling analysis the scale structure of the hypothesised LRRC-QoL revealed a number of inconsistencies within the proposed structure of the questionnaire and did not support the concept of unidimensionality. This was further confirmed through the use of factor analysis, which reproduced only one of the five hypothesised scales and produced eight new scales. Factor analysis split up the relatively big, hypothesised symptoms scale and separated it out into a more functional and logical systems based approach, by clustering items regarding the similar biological systems together. Overall, all of the newly proposed scales by factor analysis were logical and largely fulfilled the pre-requisite criteria of multitrait scaling. However, the new Stoma and Wound and the Pain and Discomfort scales were the only two new scales not to fulfil the principles of multitrait scaling analysis with Item 12 within the Stoma scale and Item 4 within the Pain scale not displaying uniformity when compared to the other items within the scale. Subsequently, these items were removed from these scales. Using this combined method of multitrait analysis and factor analysis ensured the same underlying construct was measured by each defined scale through multiple rounds of testing, thus contributing to the overall robustness of the structure of the LRRC-QoL and providing evidence for the construct validity of the questionnaire.

The LRRC-QoL demonstrated excellent temporal and scale reliability, high ICC and Cronbach's Alpha values of >0.70 for the majority of the scales. The internal consistency, using the internal item consistency (item intercorrelations) and Cronbach's Alpha provides further evidence for scale structure, by providing a further measure of homogeneity amongst the items of each scale. The ICC values confirm the ability of the LRRC-QoL to produce highly reproducible scores on repeated applications. However, given the associated size of the confidence intervals observed with these values, these results must be interpreted with caution and must reproduced within a larger sample size.

The convergent validity of the LRRC-QoL was relatively good, with the majority of *a priori hypotheses* correctly confirmed, with moderate to high correlations demonstrated between the LRRC-

QoL, the FACT-C and the EORTC CR29 questionnaires. This provides supporting evidence that the LRRC-QoL scales measure what they purport to measure. The obvious limitation in demonstrating the convergent validity of the LRRC-QoL was the exclusion of the use of the core EORTC QLQ-C30 measure. This was due to an oversight on the principal investigators part in the first round of dispatching the questionnaires and as recruitment had already commenced by the time this was realised, a pragmatic decision was made to continue the study without using the EORTC QLQ-C30 for validation purposes. Consequently, further work is required to provide further evidence for the convergence validity using the EORTC QLQ-C30, as well as demonstrating whether the LRRC-QoL can be used in conjunction with this measure. Future works should include examining a number of hypothetical correlations between these two measures including the following:

- The LRRC-QoL psychological scale would correlate ($r>0.45$) with the EORTC QLQ-C30 emotional scale.
- The LRRC-QoL pain scale would correlate ($r>0.45$) with the EORTC QLQ-C30 pain scale.
- The LRCC-QoL lower limb scale would correlate ($r>0.45$) with the EORTC QLQ-C30 physical function scale.

A further limitation of the convergence validity is the number of significant correlations that were revealed between the LRRC-QoL and the FACT-C and EORTC questionnaires, which were not previously hypothesised. A total of 5 such correlations were made, which did not make logical sense, this may be due to the multiple comparisons made between the LRRC-QoL, FACT-C and EORTC CR29 questionnaires. Consequently, further work is required regarding establishing the convergence validity of the LRRC-QoL. This should be carried out in an independent sample.

The evidence for the known groups comparison validity of the LRRC-QoL is conflicting. Although the LRRC-QoL was able to discriminate scores between some clinically relevant groups of patients, its overall ability to demonstrate any meaningful data is limited by its relatively small sample size,

which is demonstrated by the few statistically significant differences observed. This is further compounded by the variable rate of missing data regarding a number of clinical domains, which limits the available sample size further. To confirm the known groups comparison validity further work is required in a much larger sample size.

The psychometric evaluation of the LRRC-QoL was based on the traditional methods of CTT. CTT has been widely used in the development and validation of a number of colorectal PROMs which are in use in current clinical and academic practice, including FACT-C [143] and EORTC QLQ-CR29 [285]. CTT has a number of advantages including the ease with which its methods are relatively traceable through the application of statistical and mathematical modelling which can be checked against existing criteria [366]. Furthermore, the sample sizes required to run the statistical tests associated with CTT do not require large numbers [367] and are therefore ideal in relatively rare disease states such as LRRC. A further advantage of CTT is that the underlying model is ideal for multi-scale instruments whereby each scale measures the same underlying construct, with each item equally contributing to the overall scale score, which is ideally suited for the design of the LRRC-QoL. However, the CTT model does not require individual items to be optimal, items that relate modestly to the underlying variable can be used within a scale if there are a number of items which contribute to the same underlying variable. This was apparent in the initial Stoma and Wound care scale and Pain and Discomfort scales, which were formulated using the principals of factor analysis. Although, the items within these scales all loaded onto the same factor, these items failed to correlate at repeat multi-trait scaling analysis, and were therefore removed.

Despite the popularity of CTT in developing PROMS, it has a number of limitations, including the lack of precision within the model; scales can often be long and the items can be very similar in nature. This is as a consequence of requiring to develop items which correlate with one another i.e. high inter-item correlations which can potentially lead to superficial similarities between items as

opposed to a true correlation reflecting the same underlying construct. For example, irrelevant item characteristics such as grammatical structure may be common across items. This leads to the true score of the scale reflecting all the characteristics of the items, including the combination of the true variable of interest and the superficial commonalities, without being able to accurately differentiate between the two. Furthermore, CTT does not rigorously scrutinise item characteristics, which can be a potential shortcoming. Although, this is a generic criticism of CTT methods, this was not applicable to the LRRC-QoL. The majority of the items within the scales of the LRRC-QoL measured different aspects of the same underlying construct, inter-item correlations did not represent superficial commonalities and there was no repetition of items within scales.

CTT assumes that the measurement of random error (E) is normally distributed and identical for all scores and is therefore assumed to have a constant value regardless of the participants' location on the range of the scale. This leads to CTT based scales being potentially prone to differential sensitivity at the centre relative to the extremes of the score range, which translates as differences in scores at the centre of a range may represent a smaller true score difference than at the extremes [366].

CTT produces parameters that are dependent on the sample studied [366, 368]. This can yield conflicting results and impact on the measurement performance of the PROM based on its study sample. This means different population samples with different variances will potentially not yield equivalent data or data that is easily comparable across samples. This study attempts to overcome this limitation of CTT by studying patients with LRRC across a number of centres.

The overarching limitation of this study is the relatively small sample size of the patient population, with only 80 patients included in this subset analysis of British patients. The patient and clinical demographics may not be reflective of the spectrum of patients undergoing assessment and treatment

of LRRC, as a greater proportion of male patients and those treated with curative intent participated in the study. This is potentially reflected in the study results, with the known groups comparison, identifying significant relationships between gender and sexual function scale and treatment intent and stoma scale. Furthermore, the relatively small sample size can have lead to the generation of a number of type II statistical errors, as was evident when trying to determine correlational relationships between the LRRC-QoL and the EORTC CR29 and FACT-C scales, in an attempt to establish convergence validity.

A number of strategies were employed to mitigate the effects of a small sample size, including examining key aspects of the exploratory factor analysis and examining the confidence intervals for measures of reliability and validity. On assessing the communality of variables, degree of overdetermination and size of the factor loadings derived from the exploratory factor analysis, the values extracted for the LRRC-QoL highlighted the underlying strength of the data, which were adequate for determining the scale structure of the LRRC-QoL using the existing sample size of 80 patients.

The observed values derived from the measures of Cronbach's Alpha and ICC fulfilled the pre-requisite criteria for establishing the reliability of the LRRC-QoL. However, on assessing the precision of these observed values using confidence intervals revealed a number of observed values with wide confidence intervals. The precision of the observed value is therefore questionable, this is most likely due to the underlying sample size of the study. Providing the confidence intervals alongside the observed values for Cronbach's Alpha and ICC values provides a more accurate reflection of the overall reliability of the LRRC-QoL. On applying the same principles of assessing the confidence intervals for the Pearson's product correlation coefficient, the size of the confidence intervals were wide for the majority of observed values, with a significant proportion of the confidence values crossing the 0 value. Overall, the sample size used in this study to determine the

reliability of the LRRC-QoL was adequate, however further evidence for reliability could be provided by replicating this in a larger sample size to ensure precision of the observed value and to provide further robust evidence. The sample size used in this study to determine the validity of the LRRC-QoL was inadequate, small sample sizes are associated with wide confidence intervals, with reduces the precision of the observed value. The validity of the LRRC-QoL needs to be determined within a larger subset of patients demonstrating statistically significant Pearson's product moment correlations with narrow confidence intervals.

8.5 Conclusions

The proposed scale structure of the LRRC-QoL did not fulfil the principles of multi-trait scaling analysis and required further testing using exploratory factor analysis. This led to the extraction of 9 factors which performed well at subsequent multitrait scaling analysis, thus confirming the scale structure of the LRRC-QoL. The item, scale and temporal reliability of the LRRC-QoL is good, however, needs to be confirmed within a larger sample size. This study failed to establish the construct and convergence validity of the measure. Thus, further work is required to establish this within a larger sample size of patients. It is hope the combined analysis of the British and Australian cohorts will overcome some of the limitations discussed in this chapter.

9 Chapter 9 – General Discussion

9.1 Overview

The aims of this thesis were to establish the impact of LRRC on HrQoL with the specific aim to develop a LRRC specific PROM for use in clinical practice and research. This project was designed as a multicentre, international, three phase mixed methodological project. Phase I developed a conceptual framework utilising qualitative and quantitative data, Phase II focussed on design and pre-testing of the LRRC-QoL and the final Phase III evaluated the psychometric properties of the outcome measure.

9.1.1 Phase I: Development of a Conceptual Framework

Phase I established a conceptual framework using data from two systematic reviews examining HrQoL outcomes in LRRC (Chapter 2) and pelvic exenteration (Chapter 3) and patient testimony through focus groups and expert panel review (Chapter 4). This conceptual framework underpins the LRRC-QoL and consists of 6 domains and 21 sub-domains including symptoms, sexual function, psychological impact, role functioning, future perspective and healthcare services. To ensure the clinical relevance of the LRRC-QoL, domains and subdomains of the LRRC-QoL were compared with 9 existing validated PROMs in primary rectal cancer. There was little overlap between the LRRC-QoL and current existing measures, with 5.5-38.8% of the LRRC-QoL domains covered by the existing measures. This provided evidence for the requirement of a LRRC-specific PROM given the inadequacy of existing PROMS for primary colorectal cancer in capturing themes relevant to this patient population group.

9.1.2 Phase II: Development and Pre-testing of the LRRC-QoL

The LRRC-QoL was designed in keeping with the principles of the development of the EORTC questionnaires with the intention to use the LRRC-QoL as a supplementary module to the EORTC QLQ-C30. Using the EORTC item bank and a modified Delphi exercise, 39 items were operationalised into 6 scales of Symptoms, Psychological Impact, Role Function, Sexual Function, Future Perspective and Healthcare Services. This provisional questionnaire was pre-tested using cognitive interviews in 32 patients. This identified 16 items as being problematic by the British and Australian cohort due to issues with clarity, assumptions and other problems. The LRRC-QoL was modified to correct these issues. The final version of the LRRC-QoL consisted of 32 questions organised into 5 hypothesised scales; Symptoms, Sexual Function, Psychological Impact, Future Perspective and Healthcare Services.

9.1.3 Phase III: Psychometric Analysis

The LRRC-QoL was validated for use in British patients with LRRC, in an initial sample size of 80 patients (with ongoing data collection in Australia). Initial multi-trait scaling on the hypothesised scale structure of the LRRC-QoL failed to meet the principles of unidimensionality and therefore exploratory factor analysis was performed to identify a potential new scale structure. Exploratory factor analysis retained only 1 original scale (Healthcare Services) and identified 8 new scales (Psychological Impact, Sexual Function, Sexual Interest, Pain and Discomfort, Urostomy-Related Symptoms, Lower Limb Symptoms, Stoma and Wound Related Issues, Urinary Symptoms). Further multi-trait scaling analysis confirmed the unidimensionality of 6 of these 8 scales, with revision of 2 scales (Pain and Discomfort and Stoma and Wound Related Issues).

The reliability of the LRRC-QoL was assessed at a scalar and temporal level using the measures of Cronbach's Alpha and the Intra-class correlation. Cronbach's Alpha values of >0.70 were fulfilled by

the majority of the scales, except the pain and urinary symptoms scales. Temporal stability, using the test-retest measure, of the LRRC-QoL is good, with ICC values of >0.7. However, the confidence intervals were wide for the majority of obtained values due to the small sample size.

The LRRC-QoL demonstrated good construct validity as all the scales were unidimensional in measuring the same underlying construct with no overlapping measurement of constructs with the other scales, as determined by the second round of multitrait scaling analysis. The LRRC-QoL displayed reasonably good convergence validity, with 80% of the *a priori hypotheses* between the LRRC-QoL scales and the FACT-C and EORTC CR29 scales fulfilled. However, a number of correlations were seen that were not previously hypothesised. The evidence for known-groups comparisons is limited, with the LRRC-QoL being able to discriminate scores between a few clinically relevant categories, including gender and treatment intent. However, the LRRC-QoL failed to discriminate scores in the following clinical categories; presence of concurrent metastatic disease, recurrent disease location, pre-operative treatments and current disease status.

9.2 Methodological Strengths and Limitations

9.2.1 Phase I

The conceptual framework of the LRRC-QoL was developed using a variety of sources including current published literature, peer-reviewed papers, conference abstracts, unpublished grey literature, patient testimony and expert opinion. This ensured the developed conceptual framework appropriately reflected the perspectives of the LRRC population through inclusion of all potential published sources, thus ensuring the overall content validity of the measure. This is crucial to the future application of the PROM ensuring the concept of interest is truly being measured and subsequently ensuring the results captured are applicable and of value [369].

LRRC encapsulates a heterogeneous population with a variable nature of disease recurrence, both with regards to pelvic recurrence and extra-pelvic disease, which is reflected in the wide range of available treatment options including operative and oncological. To ensure the LRRC-QoL is representative and applicable to all patients with LRRC no exclusions were made to the inclusion criterion for the systematic reviews or the qualitative study with respect to clinical variables. We were unable to secure ethical approval for including patients who had undergone non-surgical palliation of their LRRC for this phase. This was due to the ethics committee being concerned about the potential psychological burden of participating in a focus group study for patients with end stage, palliative LRRC. There was, however, some representation of this patient population in the systematic review of HrQoL outcomes in LRRC (Chapter 2), as 9% of patients included underwent palliative chemotherapy +/- radiotherapy or best supportive treatment for LRRC. By ensuring appropriate inclusion of all patients with LRRC and reflecting all opinions ensures the future usability of our PROM by ensuring it possesses content validity.

However, there are some limitations to the work conducted in Phase I. The development of the conceptual framework is potentially limited by the quality and quantity of the current evidence base reporting HrQoL outcomes in patients with LRRC. A number of methodological limitations were common across studies included in both reviews, which included retrospective data collection, mixed disease populations, sampling and responder bias, long lag periods between diagnosis and/or treatment and collection of HrQoL data, lack of baseline data and the lack of use of validated measures. These limitations have obvious implications on understanding the reporting and evaluation of PROs and HrQoL in this complex disease group and further limits the understanding of the impact of LRRC on HrQoL. More importantly, these methodological limitations may have impacted upon the themes extracted, which may have potentially led to inadequacies within the conceptual framework.

Extracting PROs for patients with LRRC alone from the current evidence base was extremely difficult as the majority of studies included mixed study populations, including reporting outcomes in locally advanced primary rectal cancer, gynaecological and urological malignancy, without reporting of outcomes for individual cancer groups. A more purist approach to data extraction and development of relevant themes would have been to include studies which exclusively reported PROs in patients with LRRC. However, this would have limited the data collection and the subsequent generation of relevant themes, as only three studies would have been eligible for inclusion. Consequently, a more inclusive approach was adopted including all patients with advanced pelvic malignancies, requiring a pelvic exenteration. Despite there being considerable overlap between the themes extracted between the two reviews, it is important to note, the majority of participants in both reviews did not have LRRC, with only 52.9% (n = 501 patients) with LRRC in the first review (Chapter 2) and 3.4% (n = 20 patients) in the pelvic exenteration review (Chapter 3). As well as identifying a broad range of disease pathology within these two reviews, patients underwent a range of treatments, including surgery, radiotherapy, chemotherapy and IORT with various treatment goals. Ten of the studies outlining HrQoL outcomes in LRRC documented treatment strategies, with a total of 403 (80.4%) patients included in this review undergoing some form of surgical intervention. The number of patients undergoing palliative treatment including best supportive care included in this review was small (8.9%, n = 45). Consequently, this limits the themes extracted primarily to patients who undergo operative treatment alone and does not truly encapsulate all relevant themes for those who may undergo palliation of their LRRC. It is important to understand whether there are similarities and differences in HrQoL themes between those who undergo surgical treatment of LRRC and those who undergo palliation to enable future comparison between these important disease groups. A further limitation of the included patient population is the high number of female patients included in both reviews, with 278 (41.1%) of women included in the review of HrQoL in LRRC and 473 (80.8%) of women included in the review of HrQoL in pelvic exenteration. The inclusion of a large proportion of females has an obvious impact on the themes extracted. The majority of the work regarding sexual function and body image in both reviews was primarily conducted in female participants, with very little qualitative and quantitative work regarding sexual function and body image in male patients.

There is potential that not all relevant themes applicable to male patients have been elucidated due to the lack of inclusion of male patients within the identified studies.

The lack of adequate representation of patient and treatment factors within the sampling population combined with the methodological flaws of the studies leads to obvious limitations within the literature that has informed the inductive (top down) approach of developing the conceptual framework. The themes extracted at this stage may not have be relevant to all patients with LRRC given the heterogeneous patient population from which the evidence has been extracted. Furthermore, given the potential exclusion of important clinical groups i.e. male patients and palliative patients relevant themes may have been missed.

To overcome the limitations of relying on current evidence alone, qualitative teleconference focus groups were conducted. Teleconference focus groups were used to overcome the logistical difficulties of assembling a group due to the scattered geographical location of the majority of patients included in the study. The advantages of collecting qualitative data in this manner is the potential for data to be collected over a short time frame in a cost-effective manner [269, 370]. However, focus groups have a number of limitations including the potential for the group processes overall to have considerable influence on the consensus view expressed in the focus groups which may not be reflective of individual participants. Furthermore, the use of teleconference focus groups may lead to missing key pieces of non-verbal communication, which may potentially impact the quality of the data collect using this medium.

Given the limitations associated with focus groups, the use of in-depth cognitive interviews may have been a potential alternative in collecting qualitative data from patients with LRRC to elicit relevant concepts and themes of HrQoL. The use of in-depth cognitive interviews was considered for use in

Phase I of the LRRC-QoL. However, given the geographical location of the majority of patients and the logistical difficulties of conducting face-to-face interviews, a pragmatic decision was made to conduct teleconference focus groups. It was felt that the convenience of holding teleconference focus groups would help aid recruitment in this cohort of patients. It is acknowledged that conducting in-depth cognitive interviews on an individual basis may have the potential advantage of identifying sensitive and/or personal information, which some participants may be uncomfortable sharing in a group setting [259]. In-depth cognitive interviews allows for the interviewer to explore topics in a more detailed manner, thus garnering more qualitative data which would have informed the development of the conceptual framework overall. This may have potentially led to slightly different themes being obtained. There are a number of advantages of conducting cognitive interviews over focus groups, including the process of data analysis. It is much easier to analyse the transcripts from the cognitive interviews due to the individualised nature of these interviews. Cognitive interviews represent the opinions, thoughts and feelings of one person alone. It is, therefore easier to identify themes on an individual patient basis when analysing data extracted from cognitive interviews. In comparison, the data analysis for focus groups includes analysing individual participant data and the interaction between participants. It is important that the themes extracted from focus groups are an aggregation of the views of individual participants and not the consensus opinion of the group overall [371]. Thus ensuring that participants with opposing or differing views are appropriately represented within the data analysis. There are disadvantages associated with conducting cognitive interviews including their costly and time consuming nature [259].

9.2.2 Phase II

The design of the LRRC-QoL was broadly based on the EORTC questionnaires, using items from the EORTC item bank to operationalise the conceptual framework. Adopting this design strategy ensured the development of a well designed, clear and concise questionnaire using previously validated items. This strategy ensured that consistency was maintained between the core EORTC QLQ-C30 module

and the LRRC-QoL. The aim of this was to help reduce cognitive loads placed on participants whilst completing both questionnaires concurrently, and to enable the development of cognitive models for repetitive behaviours which are essential for navigating through instruments and formulating responses [296, 298].

To maintain the content validity throughout Phase II of the LRRC-QOL a modified Delphi study was embedded within the study design. This Delphi study enabled patients and experts the opportunity to evaluate the range of items identified which could be suitably operationalised into a provisional questionnaire using an online survey. The use of Delphi studies in this manner is an emerging concept [372, 373]. This approach allows for the validation of the initial qualitative work within a second independent sample of patients. Using an online survey to conduct a Delphi study has a number of advantages including ease of access for participants, pre-set rules to ensure every question is answered thus limiting the amount of missing data, easy and efficient collation of survey results and prompt distribution of feedback. There are, however, some limitations to our Delphi study, this includes the small overall sample size and the subsequent potential for bias as the participants who responded to the survey may not be representative of the overall population with LRRC. Furthermore, the use of an online Delphi survey limits participation to those with Internet access alone and to those who are interested in participating in research.

One of the greatest strengths of this study was the way in which the data analysis was conducted. The data analysis was conducted in the same manner in the UK and Australia, with review and analysis of all data after three consecutive cognitive interviews. This was followed by review by an expert panel. All data was coded in accordance with the QAS-99 tool. Although, the methodology employed was the same in both participating countries, the cognitive interviews and data analysis were conducted separately. The final versions of the LRRC-QoL from both countries were synthesised and reviewed by an international expert panel, prior to finalisation of the format and content of the LRRC-QoL.

This strategy ensured a systematic and robust manner of analysis was employed taking into the account the individual analyses from both participating countries and synthesising these to ensure the overall content validity of the LRRC-QoL was retained. Employing this strategy ensured the cross-cultural equivalence of the LRRC-QoL between the UK and Australia, ensuring both operational and item equivalence, thus ensuring the content validity of the measure overall. The use of a checklist, in the form of the QAS-99 tool, enabled the systematic analysis of the collected data, allowing for the easy and early identification of problematic items [312, 319, 320]. The QAS-99 has been previously reported to be the most productive method in identifying potential issues with surveys and questionnaires during the pre-testing phase, however, it has been determined to have a high sensitivity and a low specificity when discriminating between items [374]. In a bid to circumvent these issues regarding sensitivity and specificity, a dual process of analysis was employed by discussing all items highlighted by the QAS-99 checklist with an expert panel. The use of expert panels in pre-testing questionnaires has been well documented and are proven to be an effective method of identifying potential issues [374, 375]. This dual process of analysis ensured that appropriate items were being considered for revision, refinement and inclusion within the LRRC-QoL.

The overarching limitation of cognitive interviews and this manner of pretesting questionnaires are that they are entirely reliant on qualitative methodology to assess potential measurement error. Qualitative methods, including cognitive interviews, are good at identifying potential difficulties in item wording, format and responses, however they cannot quantitatively measure the size and magnitude of the identified difficulty and cannot measure whether proposed revisions have the capacity to reduce the measurement error [314]. Consequently, there has been an emergence of quantitative methods, including Rasch and Item-response theory, in pretesting questionnaires. These modern psychometric techniques assess how well items address the entire continuum of patient experience of the concept and have been used increasingly in the development and pre-testing of a number of PROMS [376-379]. The use of quantitative methods early in instrument development is aimed at providing descriptive profiles and exploratory information regarding the questionnaire

content. In comparison, confirmatory psychometric evaluation during the latter phases of PROM development are used to provide definitive information regarding the measurement properties. The use of Rasch analysis and Item-Response theory undoubtedly adds value and rigour to the pre-testing phase of questionnaire development by providing precise and accurate measures of scale performance, measuring scale construct and not scale content alone and by providing statistical detail on the measurement performance of each individual item [380, 381]. Provision of quantitative measurement data on scale operationalisation at the pre-testing stage enables for scale refinement, development and retesting in a more scientifically rigorous and robust manner than relying on qualitative methods alone. However, it must be acknowledged that quantitative methods should not be used alone as a substitute for qualitative methodology, but in tandem, in an effort to provide data which is both qualitatively and quantitatively meaningful. The use of qualitative and quantitative methodology provides the optimal foundations to fully understand the measurement performance of a questionnaire.

The lack of quantitative methods during the pre-testing stage of LRRC-QoL may potentially limit the clinical utility of the measure overall by potentially under- or over-estimating the content validity provided through the use of qualitative methodology alone. However, the LRRC-QoL has been developed in accordance with existing guidelines on the development of PROMS [89, 212, 292], including guidance from the FDA, EORTC and ISPOR. These well-regarded institutions advocate the use of qualitative methods, in particular, cognitive interviews, when pre-testing questionnaires. Therefore, the LRRC-QoL fulfils current gold standard criteria in the development of PROMs. However, as the science of PROMs continues to evolve, quantitative methodology such as Rasch or Item Response theory may become a mandatory component of pre-testing of questionnaires. To be able to reliably incorporate this into the current algorithms of developing PROMS requires guidance from the regulatory authorities, appropriate training and resource. At present, due to the lack of guidance and regulation, it is not unsurprising that researchers follow tried and tested methods of questionnaire development currently advocated by the regulatory authorities.

9.2.3 Phase III

Achieving the target recruitment for the UK cohort for Phase III is one of the strengths of this study. LRRC is a relatively rare disease outcome for primary rectal cancer, with approximately 700 patients a year being treated operatively within the UK. Given these relatively small numbers it is not unsurprising that the recruitment rate was slow and target recruitment was not met in a timely fashion, however, despite this the study eventually recruited its target sample size for the UK cohort. This is due to the regular monitoring of monthly recruitment rates, regular discussion with PIs and sites and continual review and revision of recruitment strategies. The constant reviewing and revision of recruitment strategies led to sending patients personalised letters from the lead PIs at each site, site visits and access to clinical registries. Employing these strategies enabled eventual achievement of the target sample size. The important lessons learnt from this study overall will be implemented to inform and modify the protocol to aid recruitment for the Phase III component of the Australian validation.

The main strength of Phase III was the methodological and step-wise manner in which the psychometric analysis was conducted. The use of a clear and detailed analysis plan made it easier to identify and eliminate any poorly performing items and ensured a robust scale structure. Using a combined approach of multitrait scaling and factor analysis enabled testing of the *a priori* scale structure of the LRRC-QoL and allowed for the identification of any latent scales. Both multitrait scaling analysis and exploratory factor analysis have both been previously used in combination to determine the scale structure of multi-item scales, and therefore was an ideal strategy for determining the structure of the LRRC-QoL. Multiple rounds of testing the scale structure using this method ensured that any items which did not perform optimally within a scale were appropriately identified and reviewed. This ensured the principles of unidimensionality were maintained through the scale

structure of the LRRC-QoL, so that each item within a scale measured the same underlying construct. Employing this dual strategy of testing the scale structure of the LRRC-QoL ensured the rigor and robustness of the final scale structure and therefore ensured the construct validity of the measure overall.

The LRRC-QoL was designed, developed and validated with a multi-national perspective, ensuring cross-cultural equivalence for British and Australian patients. Four areas of equivalence are required when conducting multinational research; this includes conceptual equivalence, operational equivalence, item equivalence and scalar equivalence [317]. Conceptual equivalence for the LRRC-QoL was demonstrated in Phase I by conducting focus groups in both population groups and ensuring appropriate and relevant HrQoL themes were extracted. The operational and item equivalence of the LRRC-QoL was demonstrated in Phase II, whereby the structure, format and interpretation of each item of the LRRC-QoL, was assessed individually in both populations. Although, a number of steps have been taken to ensure the LRRC-QoL is relevant and applicable to both populations, we have failed to demonstrate the scalar equivalence of the LRRC-QoL thus far. This is primarily because the final phase of this thesis reports on the psychometric analysis of the LRRC-QoL in the UK population alone. Currently, recruitment is on going in Australia. We will not be able to demonstrate the scalar equivalence of the LRRC-QoL between the two population groups until the psychometric analysis has been completed for the entire group. Therefore, at present, the LRRC-QoL does not demonstrate complete cross-cultural equivalence, and therefore, cannot be used in the Australian population.

The obvious limitation of Phase III is the sample size of the study. There are no strict rules with regards to determining the sample size for the validation of PROMS, however, for the purposes of this

study the EORTC guidance was followed [212]. This states that a subject to item ratio of 5-10 participants per item is adequate, based on this a sample size of 160 was determined for the UK and Australian cohort. However, this is a preliminary analysis of the UK cohort and therefore does not fulfill this pre-requisite criterion. To overcome the limitations of a smaller than anticipated sample size a number of strategies were employed. This included examining key aspects of the exploratory factor analysis to ensure the underlying robustness of the data was adequate for determining scale structure. Confidence intervals were examined for the measures of reliability (Cronbach's Alpha and ICC) and validity (Pearson's product moment correlation) to assess the precision of the observed value. Employing these strategies revealed the sample size was adequate to determine the scale structure of the LRRC-QoL, with acceptable communality of variables, degree of overdetermination and size of the factor loadings.

The majority of the LRRC-QoL scales were considered to be reliable according to the observed values of Cronbach's Alpha and ICC with acceptable confidence intervals suggesting the sample size to determine reliability was adequate. However, this was not applicable for all scales with wide confidence intervals observed for Cronbach's Alpha for the pain scale, lower limb symptoms scale, stoma scale, sexual interest scale and the urinary symptoms scale. Wide confidence intervals, which included the observed values were observed with the ICC for healthcare services scale, psychological impact scale, pain scale and urinary symptoms scale. This means that the reliability of the LRRC-QoL requires further testing within a larger sample size.

The lack of inclusion of the EORTC QLQ-C30 core questionnaire in the validation of the LRRC-QoL limits the ability to test convergent validity. The convergent validity of the LRRC-QoL was tested

using the FACT-C and EORTC CR29 questionnaires alone, with a number of moderate to high correlations made in the hypothesised direction. As well as a number of not previously hypothesised correlations identified. Including the EORTC QLQ-C30 would have potentially provided more evidence for the convergent validity of the LRRC-QoL, thus strengthening the evidence for this psychometric outcome. Future work surrounding convergent validity for the LRRC-QoL will need to include the EORTC QLQ C30 and will need to be conducted in an independent sample. Furthermore, the lack of inclusion of the EORTC QLQ-C30 limits the initial recommendation that the LRRC-QoL should be used as a supplementary module to the core EORTC questionnaire. The recommendation to use the LRRC-QoL in this manner can only be made following the validation of the measure using the EORTC QLQ-C30 in an independent sample.

The small sample size in this study is further compounded by the relatively high rates of missing clinical data, which further reduces the statistical power of the study. Difficulties were encountered in collecting clinical and patient demographic data from participating sites, with a number of sites failing to provide this information to the coordinating project team. This may be due to the amount and complexity of the clinical data required from sites for Phase III. Furthermore, due to the lack of standardised referral and follow up pathways for LRRC, there is often a degree of missing clinical data within the registries kept by the tertiary centres. Missing data rates are often highest for details of the primary cancer, re-recurrent disease and adjuvant oncological treatments, as these details are held by the primary, referring centre and not always communicated to the tertiary hospital. The lack of available clinical data is reflected in the analyses and results for the known groups validity. Limited numbers of patients with specific characteristics i.e. urostomy, palliative chemoradiation etc. meant

that subset analyses were not conducted for these groups and therefore we were unable to validate whether the LRRC-QoL is able to determine meaningful and discriminatory scores in these cohort of patients at present. Furthermore, the observed values for the known groups validity analyses have wide confidence intervals, further reinforcing the limitations in the interpretation of the results.

The results from Phase III of this study must be interpreted with caution as they report on an interim analysis in the UK cohort alone, which limits the generalisablity of the obtained results. Conducting an interim analysis has advantages and disadvantages. Within the context of conducting research in rare disease settings using interim analyses, within the setting of an adaptive trial design is a useful study design to ensure successful recruitment in a difficult disease cohort [382, 383]. This concept is not limited to clinical trials and has previously been explored within the context of observational studies [384]. The advantage of employing an interim analysis is that it allows for an evaluation of the study processes and its impact on data collection. Specifically, for the LRRC-QoL, we identified a lack of adequate representation in our patient population, with a greater proportion of male patients and those treated with curative intent participating in this study, with a lack of patients with a urostomy or treated with a palliative setting adequately represented. Consequently, we have modified our sampling strategy with ongoing data collection in Australia. However, there are a number of limitations associated with conducting an interim analysis, this includes the acquisition of immature results on small numbers of patients, which may provide imprecise and biased results. The results obtained from the interim analysis may differ greatly from the final obtained results and therefore are not conclusive. Furthermore, these results are not applicable or generalisable to all patients with LRRC, due to the lack of Australian data and the imbalances in the study population included.

One of the major drawbacks of this study is the lack of endorsement of the LRRC-QoL tool from the EORTC, especially given that the development and validation of this outcome measure has been based on the guidelines from this organisation. Initially, during project conceptualisation EORTC guidance and endorsement was not sought as the initial project design was broadly based on the FDA guidelines [89]. It was not until the commencement of the project that it was realised the EORTC questionnaires would make a useful template upon which to build and design the LRRC-QoL (Chapter 6). By this stage, it was too late to approach the EORTC, especially given the commencement of the work and the time constraints required to finish the thesis. The obvious advantages of working collaboratively with the EORTC would be the additional expertise available to help develop and validate the LRRC-QOL, as well as providing support in the dissemination of the end user outcome measure and badging the LRRC-QoL as an official EORTC module.

The LRRC-QoL has been validated using the principles of CTT. CTT is a traditional psychometric method which consists of a number of theoretical principles and statistical models, which derive summated scores across multiple items. CTT assumes that each observed score on a PROM is a combination of the true score of the concept of interest and unsystematic random error. The strengths of using this model to validate the LRRC-QoL include the familiarity of the statistical model in developing PROMs, the relative ease of use and its ability to provide tangible statistics that can be checked against existing criteria [368]. However, there are a number of limitations of CTT. Firstly, CTT focuses on the total scale score, with its theoretic constructs operating on the summary scores of items, consequently individual items are not considered [367]. This was apparent during the second round of multitrait scaling analysis, which identified, two items regarding wound issues and rectal discharge that had been loaded onto two different factors, Stoma and Wound scale and Pain and Discomfort scale, at exploratory factor analysis, which failed to correlate on repeat multitrait scaling analysis. Secondly, CTT produces results that are sample and scale dependent, leading to potential

drawbacks if the measurement performance of the instrument is affected by the sample it is suppose to be measuring. Thirdly, the standard error of measurement is assumed to be a constant value irrespective of the person's location of the range of the scale. These inherent limitations associated with CTT have the potential to limit the psychometric validity of the LRRC-QoL, therefore it is important that the results obtained from this analysis are confirmed within a larger sample. If at this stage further issues are identified, it may be useful to repeat the psychometric validation of the LRRC-QoL using newer psychometric techniques, such as Rasch analysis.

Conducting this study on a multi-centre platform has both advantages and disadvantages. The main advantage of conducting the validation of the LRRC-QoL in this manner is obtaining a diverse sample which is representative of the population of interest, thus making the obtained results generalisable. A further advantage of employing more than one centre which manages complex patients with LRRC is that it enables for faster recruitment due to the combined patient pool available. Although, the overall recruitment for Phase III was relatively slow, using patients from one site alone would have further impeded the recruitment rate further for this project. The main disadvantage of conducting multicentre research was the logistical aspects of coordinating a number of sites. Difficulties were encountered with obtaining local ethical approval for sites which led to a delay in opening the study for recruitment. This is a reflection of coordinating the individual processes of a number of Research and Development departments. A further disadvantage of the LRRC-QoL was the lack of 'buy-in' into the study by some of the centres, with non-engagement of the PI from one site. This was combined with difficulties encountered with gathering patient and clinical demographics from participating sites, which contributes to the moderately high rates of missing data within these domains and ultimately contributes to a reduction in the power of the study overall. As these issues were realised during the course of the study appropriate measures were taken from the central, coordinating centre, with site visits initiated, research nurses identified to help the day-to-day running of the study, regular

communication and updates from each site and on-site access to clinical registries.

9.3 Future Applications of the LRRC-QoL

The LRRC-QoL has been developed in response to a need within the colorectal fraternity to objectively, accurately and robustly measure HrQoL outcomes in patients with LRRC [6]. The development of this instrument is the first step towards achieving this.

9.3.1 Clinical Application

The potential clinical applications of the LRRC-QoL are vast and can provide unique insights into patient outcomes, processes of care and health service outcomes [250-252].

Patient Level Outcomes

The LRRC-QoL can be used in clinical practice to quantify patient symptoms, experience and overall satisfaction. Using PROMS in routine clinical practice can improve the overall reporting of symptoms, lead to the disclosure and identification of symptoms not routinely reported and improve the early detection and subsequent monitoring of symptoms. The LRRC-QoL is ideally suited for assessing symptoms in this manner as it encapsulates the wide range of potential symptoms patients can experience, and can therefore help guide clinical decision-making.

Outcome Measure

The burden of treatment for LRRC is high for patients, in particular for surgical intervention, and therefore utilising HrQoL as an additional outcome is of huge relevance in this cohort. By equating a value or a range of values to HrQoL using the LRRC-QoL and combining this data with oncological

and surgical outcome data, will ensure the presentation of a balanced and measured perspective when discussing and considering potential treatment options. The value of outcome measures and the type of outcome measure of most importance often differ between patients and clinicians, with HrQoL being of the most value to patients [385]. Consequently, combined presentation of quantitative data including HrQoL, oncological and surgical outcomes should be provided to patients when counselling for potential treatments during the decision-making process. The values derived using the LRRC-QoL can be integrated with established survival data to provide a dual 'quality of survival' measure to help guide clinicians and patients with clinical decision–making, including, type of treatment initiated and emphasis of treatment i.e. curative versus palliative.

Establishing baseline QoL values is important in complex disease settings such as LRRC, as there is much emerging evidence to suggest baseline QoL values are associated with overall survival, with poor baseline scores associated with poor overall survival [386, 387]. As well as baseline QoL scores being prognostic in a variety of malignancies, the use of serial measurements of QoL in advanced cancer can be used in a similar fashion to guide prognosis [388].

Patient Satisfaction

The use of PROMs can provide unique insights into patient satisfaction with treatment and healthcare services. A systematic review consisting of 16 studies reported a moderated to strong effect on patient satisfaction through the collection of routine PROMs in clinical practice [252]. The Healthcare Services domain of the LRRC-QoL is ideally suited to assess outcomes surrounding patient satisfaction and HrQoL in patients with LRRC. This domain focuses on the delivery of clinical care and clinical processes and therefore is well placed to measure patient satisfaction to help guide service improvement.

Patient-Clinician Communication

The use of PROMS can help identify patient concerns and subsequently guide patient-clinician communication [252]. There is some evidence that when clinicians are provided with PRO data there is improved communication with patients regarding HrQoL issues regarding emotional, social and sexual function [251]. Discussions of these issues in turn can lead to appropriate referral to psychological services and can improve the patients health status overall. A number of studies have reported on clinicians using PROM; concluding the use of PROMS can help confirm clinicians' knowledge of patients' clinical status, provision of a wider overall assessment, identification of appropriate issues for further discussion and contribution to patient management [389, 390]. Measuring PROMS using the LRRC-QoL in clinical practice may similarly help guide patient-clinician communication in the clinical setting in a bid to improve the clinical care currently provided to patients.

Processes of Care - Clinical Decision Making

PROMs data can help aid clinical decision-making by integrating PRO data with clinical data. The use of supplementary PRO data can help guide treatment and aid appropriate clinical referrals through the provision of a more complete assessment [251]. PROMs data may help guide clinical referral, in particular, for emotional and psychological support [390]. Using PROMs data in this manner has been shown to identify and facilitate earlier referral when compared to conventional clinical practice [391, 392].

Using PROMs in a systematic manner, over a longitudinal timeframe can provide unique insights into disease progression, symptom control and treatment response [393]. The LRRC-QoL can be used to assess the effectiveness of a variety of treatment strategies in LRRC, monitor treatment response and evaluate disease progression/regression by comparing baseline PROMs data to serial measurements.

Using the LRRC-QoL in this manner will allow clinicians to provide a tailored and individualised treatment strategy to all patients.

9.3.2 Health Services Outcomes

Use of healthcare services

The identification of psychological and emotional distress through the use of PROMs, leading to appropriate referral to psychological services can help reduce the frequency of routine clinical services. Ganz et al reported a reduction in use of routine healthcare services in women with breast cancer following psychosocial referral [394]. LRRC is a complex disease process with a number of healthcare professionals involved, with patients often requiring referral and treatment at tertiary hospitals. Ensuring access to appropriate treatment facilities either locally or within a tertiary referral centre based on integrated clinical and PROMs data may help streamline a patients cancer journey and can help reduce the need for multiple clinic visits.

National Health Service

The NHS has been collecting routine PROMs in four elective surgery groups including hernia repair, varicose vein surgery and hip and knee replacement as part of the NHS PROMS Programme. Using PROMS in this manner can provide unique insights into healthcare service delivery. Black et al demonstrated that despite an increase in utilisation rates of surgery over a three-year period there was no impact on the mean pre-operative severity score of symptoms in patients participating in the NHS PROMS programme [395]. This data provides a patient perspective on the commissioning of healthcare services, demonstrating patient need using PROMS data. The same data has been used to outline PROMS as a more sensitive indicator of consultant outcomes when compared to elective post-operative mortality in elective hip replacement [101]. The use of routine PROMS to inform healthcare policy in the NHS is still within its infancy. There are a number of challenges to overcome prior to the

use of PROMs to inform and develop healthcare policy and commissioning of services [396]. To ensure sustainable and meaningful collection of PROMS data to inform healthcare policy requires the appropriate measurement of data regarding on clinical practice and provider performance [397]. The integration of these two key features will ensure better quality data is collected, allow for better patient and clinician engagement and influence of healthcare policy [397].

The NHS is actively engaged in the development and measurement of PROMS for patients with cancer as part of the Five Year Forward View plan [398]. This plan outlines the development of a cancer dashboard with key outcome metrics, including PROMS, which will be used to assess patient and clinical outcomes. There is an emphasis on using good quality measures to measure PROs and QoL in patients living with and following the treatment of cancer. These outcome measures can then subsequently be used to appropriately target care and further treatment based on patient needs. The Department of Health is keen on working with a number of key stakeholders, including patients, charitable organisations and carers to develop a national metric of QoL to enable long-term evaluation. It is anticipated that this newly developed PROM will be suitable for use by a number of clinical system users, including healthcare commissioners and providers.

In the future should PROMS data be used to help measure provider performance to inform healthcare policy and the commissioning of healthcare services, the LRRC-QoL would be well placed to measure these output specifically in patients with LRRC. The Healthcare Services domain specifically focuses on the impact of clinical services on HrQoL and therefore would be a good tool to use in the assessment of clinical services and may play a role in the future in defining healthcare services for patients with LRRC.

9.3.3 Clinical Research

Currently, there are two population-based registries, BeyondTME Registry and the PelEx Collaborative, within the UK and Ireland measuring clinical outcomes in patients with advanced

pelvic oncology, including LRRC. The primary endpoint of these registries is to document clinical and oncological outcomes associated with the management of LRRC. The LRRC-QoL would be well placed to be incorporated within the frameworks of such established registries and could be used to measure HrQoL as a key secondary endpoint in this cohort of patients. The advantages of collecting PRO data in this way includes the potential to amass a relatively large volume of data over a short period of time, compare clinical demographics between responders and non-responders, and measure the change in HrQoL scores following treatment. This data can then be used in a variety of ways including prognostic modelling and in hypothesising the effectiveness and cost-effectiveness of a variety of treatments.

9.4 Future Perspectives - Methodological Developments of LRRC-QoL

9.4.1 Large Field Validation

The next step in developing the LRRC-QoL from a methodological perspective is the overall validation of the outcome measure in the British and Australian cohort. This large-scale validation of the LRRC-QoL in this combined population, based on the original sample size estimation of 160 patients, will identify whether the LRRC-QoL is a reliable and valid outcome measure. The findings from this combined validation of the LRRC-QoL should be further confirmed in an independent sample to ensure the generalisability of the results obtained.

9.4.2 Responsiveness

For a PROM to be used within the clinical context it must be able to accurately and appropriately detect a clinically meaningful change [276, 283, 399]. This is a measure of responsiveness. Responsiveness is an essential property of any PROM monitoring clinical changes over a longitudinal timeframe. The best way of assessing responsiveness for the LRRC-QoL would be through a multi-

centre, prospective, longitudinal study with regular interval assessment of HrQoL. Measuring the responsiveness of the LRRC-QoL will improve its utility both in clinical practice and clinical research, as this would enable the precise evaluation of treatment impact on patients, determine the minimal clinically important difference and enable for the generation of sample size calculations for future studies.

9.4.3 Further Psychometric Validation - Rasch Analysis

The LRRC-QoL was validated using the principles of CTT. Although, widely recognised for its use in the development of PROMs, there are a number of associated limitations with employing this manner of psychometric testing. To build on the initial psychometric analysis of the LRRC-QoL, further work should be carried out to refine and strengthen the validity of the LRRC-QoL using newer approaches, such as Rasch analysis. Rasch analysis is a probabilistic, mathematical model of how participants respond to any given item. It assumes that the probability of a participant endorsing an item is a logistic function of the relative difference between the item's location (how difficult the item is) and the person's location (persons' ability). The Rasch model constructs a line of measurement with the items placed hierarchically on this line according to their importance to patients. The overall objective of the analysis is to test the extent to which the observed pattern of item responses conforms to Rasch model expectations [400, 401].

Rasch analysis overcomes a number of the limitations inherent to CTT by providing item level data through the assessment of individual item function, including to what level of the underlying trait is measured by the item and the extent to which the item is related to the underlying construct measured by the instrument. It facilitates the development of a more efficient and streamlined questionnaire by reducing the number of items needed to provide comparable measurement precision and reliability. Rasch has the ability to investigate variations in item and scale performance within different

population samples [402, 403]. Therefore, future analyses of employing the principles of Rasch analysis should include overall model fit statistics (targeting of samples to items, tests of individual item fit, item-trait chi-squared vales, item characteristics curves), person separation index, ordering of response categories and differential item functioning [404].

However, the limitations of Rasch must be acknowledged prior to embarking on psychometric validation using this method. The main limitation of Rasch analysis is the relatively large sample size required to validate a multi-item PROM, with a stipulated recommendation of 10 subjects per response category [405]. There is emerging evidence that Rasch analysis requires sample sizes of between 250-500 participants to be able to ensure stable and robust estimates of item parameters [381, 405]. Given the difficulties encountered in achieving the pre-requisite sample size for the LRRC-QoL it is unlikely a sample size adequate for Rasch analysis will be realised in a timely fashion for this cohort of patients, without collaboration from a greater number of international centres.

Using Rasch analysis to supplement the initial CTT psychometric analysis conducted will help further confirm the psychometric properties of the LRRC-QoL. It may potentially help refine the PROM further, developing a shorter more robust outcome measure. This will help enhance the clinical utility of the LRRC-QoL overall.

9.4.4 International Collaboration, Translation and Cross-Cultural Validation

A number of international groups of experts have come together through the BeyondTME collaborative to develop clinical guidelines in a bid to aid clinical decision-making and to improve clinical and PRO outcomes in LRRC [6]. To effectively identify further areas of clinical research and to conduct well-designed clinical studies in LRRC requires collaborative effort between a number of clinical bodies due to the complex nature of LRRC and its relative rare occurrence. The collaborative

efforts of the LRRC-QoL between the UK and Australian team have demonstrated the advantages and pitfalls of conducting research in this cohort of patients. This study has highlighted the importance of collaborative networks in ensuring high quality delivery of clinical research in complex and rare disease processes and therefore it is imperative that further research continues in the same collaborative manner.

We have been approached by a number of clinicians and surgeons across Europe (Denmark, Norway, France, Germany) to validate the questionnaire in their respective languages and cultures. We are currently in the process of developing a protocol for the translation and field testing of the LRRC-QoL into a number of languages. To improve and strengthen the utility of the LRRC-QoL, we will approach the EORTC organisation to help advise, endorse and incorporate the LRRC-QoL within the framework of the EORTC questionnaires.

9.4.5 Online Administration, Social Media and Mobile Technology Applications

The interface between the internet, mobile technology applications and healthcare is rapidly changing and gaining increasing momentum with the rapid expansion of these technologies into diagnostics, imaging and therapeutics. The use of mobile applications through the use of text messaging and smart phone applications has been demonstrated to be effective when promoting smoking cessation [406], medication adherence [407] and overall healthcare promotion. Furthermore, the development of mobile applications which enable self-monitoring have been found to be acceptable to patients. The gradual integration of the Internet and mobile technology into healthcare has led to the development of Electronic PROMS. These are PROMS which have developed to be delivered on an online or electronic platform. Electronic PROMs offer a number of advantages over the traditional paper-based methodology including the collection of a more complete data set and the minimisation of potential sources of errors through automated calculation of scores. It also provides a more convenient method

of participation and may lead to potentially higher retention rates. Electronic PROMS can be linked with clinical registries, thus reporting data in a more clinically meaningful manner, providing data in real-time, which may help inform on going treatment strategies [130, 408]. Electronic PROMS are ideally suited to monitoring patients over a wide geographical location at timely and regular intervals. Developing an electronic version of the LRRC-QoL would potentially increase the accessibility of the measure to a wider pool of patients and would make the PROM more easier to disseminate on an international platform. However, electronic PROMS are in their infancy and for them to become widely used and embedded within the healthcare system requires the development of sophisticated information technology systems alongside the appropriate training of clinicians.

The use of social media to collect PROMS data is a relatively new and unique concept [409, 410]. Collecting PROMS data in this manner has a number of advantages including a large patient population pool, low costs and a relatively short latency period for data acquisition. This is ideally suited for measuring outcomes in rare disease groups, such as LRRC. The LRRC-QoL has the potential to be disseminated through social media using a targeted sampling strategy to identify relevant online patient groups on an international platform. Measuring PROs for LRRC in this manner allows for the acquisition of a large volume of data over a short period of time on an international platform to provide a cross-sectional representation of HrQoL in this cohort of patients. However, there are limitations to potentially using the LRRC-QoL in this manner, including sampling bias and potential lack of construct validity [410]. The potential for sampling bias occurs as participants engaging in social media are often self-selected, highly motivated individuals with familiarity in using technology and social media, and thus may not be representative of the population overall. Furthermore, it is difficult to elicit important information regarding clinical, operative and oncological outcomes and therefore has an impact on the ability to interpret the results in a clinically meaningful manner.

9.4.6 Core Outcome Set for LRRC

As demonstrated in this thesis there is significant heterogeneity in reporting PROs in LRRC. This issue of variation in outcome reporting extends to the clinical, surgical and oncological outcomes reported for this cohort of patients. This outcome heterogeneity contributes to reporting bias and prevents adequate evidence synthesis. To overcome such issues there has been much work conducted on developing core outcome sets. This work was initiated and developed by the COMET (Core Outcome Measures in Effectiveness Trials) initiative, which aims to develop a standardised set of outcomes which should be measured and reported in all trials for a particular disease pathology [411]. A core outcome set has been developed for colorectal cancer [412-414] however, this focuses primarily on primary colorectal cancer and fails to encapsulate clinical and oncological detail relevant to LRRC. It is therefore essential that a core outcome set is specifically developed for use in LRRC. This core outcome set should include PROs, which makes it ideal to embed the LRRC-QoL within its framework. This core outcome set should be developed in collaboration with key stakeholders including patients, surgeons, oncologists, specialist nurses and palliative care physicians. The development of a core outcome set in LRRC will standardise outcome reporting, enable comparison between individual studies and allow for better evidence synthesis.

9.5 Conclusions

This thesis aimed to develop and validate a PROM of HrQoL in patients with LRRC – The LRRC-QoL. This is the first measure to be developed exclusively in this cohort of patients. This PROM has been developed and validated in a methodologically robust, step-wise manner based on existing guidelines. Currently, the measure has only been validated in the UK cohort, with on-going validation in the Australian cohort. This thesis provides evidence that PROMs can be developed in complex and rare disease settings through multi-centre, international collaboration. There are number of further methodological studies which will further refine and validate the LRRC-QoL, including the completion of the Australian validation, further validation in an independent sample and assessment

of responsiveness over a longitudinal timeframe. These further studies will enhance the robustness and utility of the LRRC-QoL and make it a more relevant and applicable PROM for use in clinical practice and research. The LRRC-QoL provides a method of comprehensive assessment of the impact of LRRC and its subsequent treatments on patients and enables that impact to be quantified in a meaningful and measurable manner. It is hoped the integration of the LRRC-QoL into routine clinical practice will enable the documentation of PROs relevant to this cohort of patients through validated means. It is hoped the LRRC-QoL will be used in routine clinical practice, within the wider NHS and in clinical research as an end outcome measure in prospective clinical studies and trials. The LRRC-QoL has great potential to enhance the understanding of HrQoL outcomes and subsequently improve the clinical outcomes in this complex cohort of patients.

References

1. van Gijn W, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011; 12: 575-582.
2. Heald RJ, Moran BJ, Ryall RD et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998; 133: 894-899.
3. Kapiteijn E, Kranenbarg EK, Steup WH et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. Eur J Surg 1999; 165: 410-420.
4. Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373: 811-820.
5. Harji DP, Griffiths B, McArthur DR, Sagar PM. Current UK management of locally recurrent rectal cancer. Colorectal Dis 2012; 14: 1479-1482.
6. Beyond TMEC. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg 2013; 100: E1-33.
7. van de Velde CJ, Boelens PG, Tanis PJ et al. Experts reviews of the multidisciplinary consensus conference colon and rectal cancer 2012: Science, opinions and experiences from the experts of surgery. Eur J Surg Oncol 2013.
8. Boyle KM, Sagar PM, Chalmers AG et al. Surgery for locally recurrent rectal cancer. Dis Colon Rectum 2005; 48: 929-937.
9. Hansen MH, Balteskard L, Dorum LM et al. Locally recurrent rectal cancer in Norway. Br J Surg 2009; 96: 1176-1182.
10. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol 2007; 14: 447-454.
11. Suzuki K, Dozois RR, Devine RM et al. Curative reoperations for locally recurrent rectal cancer. Dis Colon Rectum 1996; 39: 730-736.
12. Moore HG, Shoup M, Riedel E et al. Colorectal cancer pelvic recurrences: determinants of resectability. Dis Colon Rectum 2004; 47: 1599-1606.
13. Wanebo HJ, Antoniuk P, Koness RJ et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. Dis Colon Rectum 1999; 42: 1438-1448.
14. NICE. Colorectal Cancer: Diagnosis and Management (CG131). https://www.nice.org.uk/guidance/cg131/chapter/1-Recommendations - management-of-metastatic-disease 2014.
15. Bhangu A, Ali SM, Darzi A et al. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. Colorectal Dis 2012; 14: 1457-1466.
16. Harris CA, Solomon MJ, Heriot AG et al. The Outcomes and Patterns of Treatment Failure After Surgery for Locally Recurrent Rectal Cancer. Ann Surg 2016; 264: 323-329.
17. Nielsen MB, Rasmussen PC, Lindegaard JC, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. Colorectal Dis 2012; 14: 1076-1083.
18. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. Colorectal Dis 2011; 13: 732-742.

19. Harji DP, Griffiths B, McArthur DR, Sagar PM. Surgery for recurrent rectal cancer: higher and wider? Colorectal Dis 2013; 15: 139-145.
20. Dozois EJ, Privitera A, Holubar SD et al. High sacrectomy for locally recurrent rectal cancer: Can long-term survival be achieved? J Surg Oncol 2011; 103: 105-109.
21. Zacherl J, Schiessel R, Windhager R et al. Abdominosacral resection of recurrent rectal cancer in the sacrum. Dis Colon Rectum 1999; 42: 1035-1039; discussion 1039-1040.
22. Milne T, Solomon MJ, Lee P et al. Sacral resection with pelvic exenteration for advanced primary and recurrent pelvic cancer: a single-institution experience of 100 sacrectomies. Dis Colon Rectum 2014; 57: 1153-1161.
23. Nielsen MB, Rasmussen P, Keller J, Laurberg S. Preliminary experience with external hemipelvectomy for locally advanced and recurrent pelvic carcinoma. Colorectal Dis 2012; 14: 152-156.
24. Austin KK, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. Dis Colon Rectum 2009; 52: 1223-1233.
25. Shaikh I, Aston W, Hellawell G et al. Extended lateral pelvic sidewall excision (ELSiE): an approach to optimize complete resection rates in locally advanced or recurrent anorectal cancer involving the pelvic sidewall. Tech Coloproctol 2014; 18: 1161-1168.
26. Lopez MJ, Luna-Perez P. Composite pelvic exenteration: is it worthwhile? Ann Surg Oncol 2004; 11: 27-33.
27. Miner TJ, Jaques DP, Paty PB et al. Symptom control in patients with locally recurrent rectal cancer. Ann Surg Oncol 2003; 10: 72-79.
28. Verrees JF, Fernandez-Trigo V, Sugarbaker PH. Rectal cancer recurrence after prior resection and radiotherapy: palliation following additional surgery. Int J Colorectal Dis 1996; 11: 211-216.
29. Llaguna OH, Calvo BF, Stitzenberg KB et al. Utilization of interventional radiology in the postoperative management of patients after surgery for locally advanced and recurrent rectal cancer. Am Surg 2011; 77: 1086-1090.
30. Ireland. AoCoGBa. National Bowel Cancer Audit Progress Report 2014. In. 2014.
31. Mohiuddin M, Lingareddy V, Rakinic J, Marks G. Reirradiation for rectal cancer and surgical resection after ultra high doses. Int J Radiat Oncol Biol Phys 1993; 27: 1159-1163.
32. Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. Cancer 2002; 95: 1144-1150.
33. Mohiuddin M, Marks GM, Lingareddy V, Marks J. Curative surgical resection following reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997; 39: 643-649.
34. Valentini V, Morganti AG, Gambacorta MA et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys 2006; 64: 1129-1139.
35. Das P, Delclos ME, Skibber JM et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. Int J Radiat Oncol Biol Phys 2010; 77: 60-65.
36. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997; 38: 785-790.
37. Gunderson LL, Martin JK, Beart RW et al. Intraoperative and external beam irradiation for locally advanced colorectal cancer. Ann Surg 1988; 207: 52-60.
38. Lanciano RM, Calkins AR, Wolkov HB et al. A phase I/II study of intraoperative radiotherapy in advanced unresectable or recurrent carcinoma of the rectum: a Radiation Therapy Oncology Group (RTOG) study. J Surg Oncol 1993; 53: 20-29.
39. Kallinowski F, Eble MJ, Buhr HJ et al. Intraoperative radiotherapy for primary and recurrent rectal cancer. Eur J Surg Oncol 1995; 21: 191-194.
40. Bussieres E, Gilly FN, Rouanet P et al. Recurrences of rectal cancers: results of a multimodal approach with intraoperative radiation therapy. French Group of IORT. Intraoperative Radiation Therapy. Int J Radiat Oncol Biol Phys 1996; 34: 49-56.

41. Magrini S, Nelson H, Gunderson LL, Sim FH. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. Dis Colon Rectum 1996; 39: 1-9.
42. Tveit KM, Wiig JN, Olsen DR et al. Combined modality treatment including intraoperative radiotherapy in locally advanced and recurrent rectal cancer. Radiother Oncol 1997; 44: 277-282.
43. Harrison LB, Minsky BD, Enker WE et al. High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1998; 42: 325-330.
44. Eble MJ, Lehnert T, Treiber M et al. Moderate dose intraoperative and external beam radiotherapy for locally recurrent rectal carcinoma. Radiother Oncol 1998; 49: 169-174.
45. Mannaerts GH, Martijn H, Crommelin MA et al. Intraoperative electron beam radiation therapy for locally recurrent rectal carcinoma. Int J Radiat Oncol Biol Phys 1999; 45: 297-308.
46. Pezner RD, Chu DZ, Wagman LD et al. Resection with external beam and intraoperative radiotherapy for recurrent colon cancer. Arch Surg 1999; 134: 63-67.
47. Nag S, Martinez-Monge R, Martin EW. Intraoperative electron beam radiotherapy in recurrent colorectal carcinoma. J Surg Oncol 1999; 72: 66-71.
48. Mannaerts GH, Rutten HJ, Martijn H et al. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. Dis Colon Rectum 2001; 44: 1749-1758.
49. Pezner RD, Chu DZ, Ellenhorn JD. Intraoperative radiation therapy for patients with recurrent rectal and sigmoid colon cancer in previously irradiated fields. Radiother Oncol 2002; 64: 47-52.
50. Vermaas M, Nuyttens JJ, Ferenschild FT et al. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. Radiother Oncol 2008; 87: 357-360.
51. Suzuki K, Gunderson LL, Devine RM et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer 1995; 75: 939-952.
52. Nag S, Martinez-Monge R, Mills J et al. Intraoperative high dose rate brachytherapy in recurrent or metastatic colorectal carcinoma. Ann Surg Oncol 1998; 5: 16-22.
53. Lowy AM, Rich TA, Skibber JM et al. Preoperative infusional chemoradiation, selective intraoperative radiation, and resection for locally advanced pelvic recurrence of colorectal adenocarcinoma. Ann Surg 1996; 223: 177-185.
54. Willett CG, Shellito PC, Tepper JE et al. Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 1991; 9: 843-849.
55. Wallace HJ, 3rd, Willett CG, Shellito PC et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. J Surg Oncol 1995; 60: 122-127.
56. Gunderson LL, Nelson H, Martenson JA et al. Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Dis Colon Rectum 1996; 39: 1379-1395.
57. Valentini V, Morganti AG, De Franco A et al. Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma: prognostic factors and long term outcome. Cancer 1999; 86: 2612-2624.
58. Hashiguchi Y, Sekine T, Sakamoto H et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. Dis Colon Rectum 1999; 42: 886-893; discussion 893-885.
59. Wiig JN, Poulsen JP, Tveit KM et al. Intra-operative irradiation (IORT) for primary advanced and recurrent rectal cancer. a need for randomised studies. Eur J Cancer 2000; 36: 868-874.
60. Alektiar KM, Zelefsky MJ, Paty PB et al. High-dose-rate intraoperative brachytherapy for recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 2000; 48: 219-226.
61. Haddock MG, Gunderson LL, Nelson H et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. Int J Radiat Oncol Biol Phys 2001; 49: 1267-1274.
62. Lindel K, Willett CG, Shellito PC et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. Radiother Oncol 2001; 58: 83-87.

63. Wiig JN, Tveit KM, Poulsen JP et al. Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. Radiother Oncol 2002; 62: 207-213.
64. Shoup M, Guillem JG, Alektiar KM et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. Dis Colon Rectum 2002; 45: 585-592.
65. Haddock MG, Nelson H, Donohue JH et al. Intraoperative electron radiotherapy as a component of salvage therapy for patients with colorectal cancer and advanced nodal metastases. Int J Radiat Oncol Biol Phys 2003; 56: 966-973.
66. Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. Surg Oncol Clin N Am 2003; 12: 993-1013, ix.
67. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2004; 58: 106-112.
68. Dresen RC, Gosens MJ, Martijn H et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol 2008; 15: 1937-1947.
69. Kusters M, Dresen RC, Martijn H et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2009; 75: 1444-1449.
70. Haddock MG, Miller RC, Nelson H et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 2011; 79: 143-150.
71. Wiggers T, de Vries MR, Veeze-Kuypers B. Surgery for local recurrence of rectal carcinoma. Dis Colon Rectum 1996; 39: 323-328.
72. Bedrosian I, Giacco G, Pederson L et al. Outcome after curative resection for locally recurrent rectal cancer. Dis Colon Rectum 2006; 49: 175-182.
73. Garcia-Aguilar J, Cromwell JW, Marra C et al. Treatment of locally recurrent rectal cancer. Dis Colon Rectum 2001; 44: 1743-1748.
74. Ogunbiyi OA, McKenna K, Birnbaum EH et al. Aggressive surgical management of recurrent rectal cancer--is it worthwhile? Dis Colon Rectum 1997; 40: 150-155.
75. Gunderson LL, Martin JK, Kvols LK et al. Intraoperative and external beam irradiation +/- 5-FU for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 1987; 13: 319-329.
76. Goes RN, Beart RW, Jr., Simons AJ et al. Use of brachytherapy in management of locally recurrent rectal cancer. Dis Colon Rectum 1997; 40: 1177-1179.
77. Hannoun-Levi JM, Cowen D, Houvenaeghel G et al. Preliminary results of a phase I/II study of post-operative high-dose rate brachytherapy for advanced or recurrent pelvic tumours. Eur J Surg Oncol 1997; 23: 532-537.
78. Martinez-Monge R, Nag S, Martin EW. 125Iodine brachytherapy for colorectal adenocarcinoma recurrent in the pelvis and paraortics. Int J Radiat Oncol Biol Phys 1998; 42: 545-550.
79. Minsky BD, Cohen AM, Fass D et al. Intraoperative brachytherapy alone for incomplete resected recurrent rectal cancer. Radiother Oncol 1991; 21: 115-120.
80. Kuehne J, Kleisli T, Biernacki P et al. Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. Dis Colon Rectum 2003; 46: 895-899.
81. Martinez-Monge R, Nag S, Martin EW. Three different intraoperative radiation modalities (electron beam, high-dose-rate brachytherapy, and iodine-125 brachytherapy) in the adjuvant treatment of patients with recurrent colorectal adenocarcinoma. Cancer 1999; 86: 236-247.
82. Wang JJ, Yuan HS, Li JN et al. CT-guided radioactive seed implantation for recurrent rectal carcinoma after multiple therapy. Med Oncol 2010; 27: 421-429.
83. Kim MS, Choi C, Yoo S et al. Stereotactic body radiation therapy in patients with pelvic recurrence from rectal carcinoma. Jpn J Clin Oncol 2008; 38: 695-700.

84. Dewas S, Bibault JE, Mirabel X et al. Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results. Radiat Oncol 2011; 6: 77.
85. Harji DP, Sagar PM. Advancing the surgical treatment of locally recurrent rectal cancer. Br J Surg 2012; 99: 1169-1171.
86. Anderson RT, Aaronson NK, Wilkin D. Critical review of the international assessments of health-related quality of life. Qual Life Res 1993; 2: 369-395.
87. de Haan R, Aaronson N, Limburg M et al. Measuring quality of life in stroke. Stroke 1993; 24: 320-327.
88. Macefield RC, Avery KN, Blazeby JM. Integration of clinical and patient-reported outcomes in surgical oncology. Br J Surg 2013; 100: 28-37.
89. Health USDo, Human Services FDACfDE, Research et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006; 4: 79.
90. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res 1993; 2: 153-159.
91. Patrick DL, Bergner M. Measurement of health status in the 1990s. Annu Rev Public Health 1990; 11: 165-183.
92. Read JL, Quinn RJ, Hoefer MA. Measuring overall health: an evaluation of three important approaches. J Chronic Dis 1987; 40 Suppl 1: 7S-26S.
93. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273: 59-65.
94. Darzi A. High Quality Care For All: NHS next stage review final report. Cm 7432. London: the Stationery Office. Available at: http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_085828.pdf (accessed on 29 November 2013).
95. Equity and Excellence: Liberating the NHS. In.
96. NHS Choices: Delivering for the NHS. In.
97. Neuburger J, Hutchings A, van der Meulen J, Black N. Using patient-reported outcomes (PROs) to compare the providers of surgery: does the choice of measure matter? Med Care 2013; 51: 517-523.
98. Browne J, Jamieson L, Lewsey J et al. Case-mix & patients' reports of outcome in Independent Sector Treatment Centres: Comparison with NHS providers. BMC Health Serv Res 2008; 8: 78.
99. Chard J, Kuczawski M, Black N et al. Outcomes of elective surgery undertaken in independent sector treatment centres and NHS providers in England: audit of patient outcomes in surgery. BMJ 2011; 343: d6404.
100. Gutacker N, Bojke C, Daidone S et al. Hospital variation in patient-reported outcomes at the level of EQ-5D dimensions: evidence from England. Med Decis Making 2013; 33: 804-818.
101. Varagunam M, Hutchings A, Black N. Do patient-reported outcomes offer a more sensitive method for comparing the outcomes of consultants than mortality? A multilevel analysis of routine data. BMJ Qual Saf 2015; 24: 195-202.
102. Lindgren JV, Wretenberg P, Karrholm J et al. Patient-reported outcome is influenced by surgical approach in total hip replacement: a study of the Swedish Hip Arthroplasty Register including 42,233 patients. Bone Joint J 2014; 96-B: 590-596.
103. Langenhoff BS, Krabbe PF, Wobbes T, Ruers TJ. Quality of life as an outcome measure in surgical oncology. Br J Surg 2001; 88: 643-652.
104. Trask PC, Hsu MA, McQuellon R. Other paradigms: health-related quality of life as a measure in cancer treatment: its importance and relevance. Cancer J 2009; 15: 435-440.
105. Ganz PA, Goodwin PJ. Health-related quality of life measurement in symptom management trials. J Natl Cancer Inst Monogr 2007; 47-52.

106. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr 2007; 16-21.
107. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. Lancet 2009; 374: 369-370.
108. Wu AW, Snyder C. Getting ready for patient-reported outcomes measures (PROMs) in clinical practice. Healthc Pap 2011; 11: 48-53; discussion 55-48.
109. Montgomery v Lanarkshire Health Board 2015 UKSC 11.
110. McNair AG, MacKichan F, Donovan JL et al. What surgeons tell patients and what patients want to know before major cancer surgery: a qualitative study. BMC Cancer 2016; 16: 258.
111. McNair AG, Brookes ST, Kinnersley P, Blazeby JM. What surgeons should tell patients with oesophago-gastric cancer: a cross sectional study of information needs. Eur J Surg Oncol 2013; 39: 1278-1286.
112. Devlin N, Appleby, J. Getting the Most out of PROMs: Putting Health Outcomes at the Heart of NHS Decision Making, London: The King's Fund, 2009. In.
113. Smith PC, Street AD. On the uses of routine patient-reported health outcome data. Health Econ 2013; 22: 119-131.
114. Coronini-Cronberg S, Appleby J, Thompson J. Application of patient-reported outcome measures (PROMs) data to estimate cost-effectiveness of hernia surgery in England. J R Soc Med 2013; 106: 278-287.
115. Appleby J, Poteliakhoff E, Shah K, Devlin N. Using patient-reported outcome measures to estimate cost-effectiveness of hip replacements in English hospitals. J R Soc Med 2013; 106: 323-331.
116. Dinan MA, Compton KL, Dhillon JK et al. Use of patient-reported outcomes in randomized, double-blind, placebo-controlled clinical trials. Med Care 2011; 49: 415-419.
117. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin Trials 2004; 25: 535-552.
118. Sanders C, Egger M, Donovan J et al. Reporting on quality of life in randomised controlled trials: bibliographic study. BMJ 1998; 317: 1191-1194.
119. Vodicka E, Kim K, Devine EB et al. Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007-2013). Contemp Clin Trials 2015.
120. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. Contemp Clin Trials 2009; 30: 289-292.
121. Gondek K, Sagnier PP, Gilchrist K, Woolley JM. Current status of patient-reported outcomes in industry-sponsored oncology clinical trials and product labels. J Clin Oncol 2007; 25: 5087-5093.
122. Bruner DW. Outcomes research in cancer symptom management trials: the Radiation Therapy Oncology Group (RTOG) conceptual model. J Natl Cancer Inst Monogr 2007; 12-15.
123. Bruner DW, Bryan CJ, Aaronson N et al. Issues and challenges with integrating patient-reported outcomes in clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. J Clin Oncol 2007; 25: 5051-5057.
124. Sloan JA, Berk L, Roscoe J et al. Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. J Clin Oncol 2007; 25: 5070-5077.
125. Johnson JR, Temple R. Food and Drug Administration requirements for approval of new anticancer drugs. Cancer Treat Rep 1985; 69: 1155-1159.
126. Bottomley A, Aaronson NK, European Organisation for R, Treatment of C. International perspective on health-related quality-of-life research in cancer clinical trials: the European Organisation for Research and Treatment of Cancer experience. J Clin Oncol 2007; 25: 5082-5086.
127. Drummond FJ, Kinnear H, Donnelly C et al. Establishing a population-based patient-reported outcomes study (PROMs) using national cancer registries across two jurisdictions: the Prostate Cancer Treatment, your experience (PiCTure) study. BMJ Open 2015; 5: e006851.

128. Arora NK, Hamilton AS, Potosky AL et al. Population-based survivorship research using cancer registries: a study of non-Hodgkin's lymphoma survivors. J Cancer Surviv 2007; 1: 49-63.
129. Glaser AW, Fraser LK, Corner J et al. Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open 2013; 3.
130. Ashley L, Jones H, Forman D et al. Feasibility test of a UK-scalable electronic system for regular collection of patient-reported outcome measures and linkage with clinical cancer registry data: the electronic Patient-reported Outcomes from Cancer Survivors (ePOCS) system. BMC Med Inform Decis Mak 2011; 11: 66.
131. van de Poll-Franse LV, Horevoorts N, van Eenbergen M et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011; 47: 2188-2194.
132. Thong MS, Mols F, Stein KD et al. Population-based cancer registries for quality-of-life research: a work-in-progress resource for survivorship studies? Cancer 2013; 119 Suppl 11: 2109-2123.
133. Breckenridge K, Bekker HL, Gibbons E et al. How to routinely collect data on patient-reported outcome and experience measures in renal registries in Europe: an expert consensus meeting. Nephrol Dial Transplant 2015.
134. Wright SP. Reporting on quality of life in RCTs. CONSORT guidelines should be expanded. BMJ 1999; 318: 1142.
135. Brundage M, Bass B, Davidson J et al. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. Qual Life Res 2011; 20: 653-664.
136. Rees JR, Whale K, Fish D et al. Patient-reported outcomes in randomised controlled trials of colorectal cancer: an analysis determining the availability of robust data to inform clinical decision-making. J Cancer Res Clin Oncol 2015.
137. Lee CW, Chi KN. The standard of reporting of health-related quality of life in clinical cancer trials. J Clin Epidemiol 2000; 53: 451-458.
138. Efficace F, Bottomley A. Health related quality of life assessment methodology and reported outcomes in randomised controlled trials of primary brain cancer patients. Eur J Cancer 2002; 38: 1824-1831.
139. Efficace F, Bottomley A, Osoba D et al. Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials--does HRQOL evaluation in prostate cancer research inform clinical decision making? J Clin Oncol 2003; 21: 3502-3511.
140. Efficace F, Osoba D, Gotay C et al. Has the quality of health-related quality of life reporting in cancer clinical trials improved over time? Towards bridging the gap with clinical decision making. Ann Oncol 2007; 18: 775-781.
141. Kyte D, Duffy H, Fletcher B et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. PLoS One 2014; 9: e110229.
142. Calvert M, Brundage M, Jacobsen PB et al. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. Health Qual Life Outcomes 2013; 11: 184.
143. Ward WL, Hahn EA, Mo F et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Qual Life Res 1999; 8: 181-195.
144. Gujral S, Conroy T, Fleissner C et al. Assessing quality of life in patients with colorectal cancer: an update of the EORTC quality of life questionnaire. Eur J Cancer 2007; 43: 1564-1573.
145. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. Eur J Cancer 1999; 35: 238-247.

146. Cheung WY, Garratt AM, Russell IT, Williams JG. The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. development and validation. J Clin Epidemiol 2000; 53: 297-306.
147. Rockwood TH, Church JM, Fleshman JW et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum 2000; 43: 9-16; discussion 16-17.
148. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut 1999; 44: 77-80.
149. Groll D, Vanner SJ, Depew WT et al. The IBS-36: a new quality of life measure for irritable bowel syndrome. Am J Gastroenterol 2002; 97: 962-971.
150. Krarup AL, Peterson E, Ringstrom G et al. The Short Health Scale: A Simple, Valid, Reliable, and Responsive Way of Measuring Subjective Health in Patients With Irritable Bowel Syndrome. J Clin Gastroenterol 2014.
151. Kennedy RH, Francis A, Dutton S et al. EnROL: a multicentre randomised trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme. BMC Cancer 2012; 12: 181.
152. Keller DS, Ermlich BO, Schiltz N et al. The effect of transversus abdominis plane blocks on postoperative pain in laparoscopic colorectal surgery: a prospective, randomized, double-blind trial. Dis Colon Rectum 2014; 57: 1290-1297.
153. Bartels SA, Gardenbroek TJ, Aarts M et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. Br J Surg 2015; 102: 281-287.
154. Russell MM, Ganz PA, Lopa S et al. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04. Ann Surg 2015; 261: 144-148.
155. Brown SR, Mathew R, Keding A et al. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg 2014; 259: 916-923.
156. Senapati A, Gray RG, Middleton LJ et al. PROSPER: a randomised comparison of surgical treatments for rectal prolapse. Colorectal Dis 2013; 15: 858-868.
157. Juul T, Ahlberg M, Biondo S et al. Low anterior resection syndrome and quality of life: an international multicenter study. Dis Colon Rectum 2014; 57: 585-591.
158. Biondo S, Golda T, Kreisler E et al. Outpatient versus hospitalization management for uncomplicated diverticulitis: a prospective, multicenter randomized clinical trial (DIVER Trial). Ann Surg 2014; 259: 38-44.
159. Pucciarelli S, Del Bianco P, Efficace F et al. Patient-reported outcomes after neoadjuvant chemoradiotherapy for rectal cancer: a multicenter prospective observational study. Ann Surg 2011; 253: 71-77.
160. Stephens RJ, Thompson LC, Quirke P et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol 2010; 28: 4233-4239.
161. van Hooft JE, Bemelman WA, Oldenburg B et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. Lancet Oncol 2011; 12: 344-352.
162. von Wagner C, Ghanouni A, Halligan S et al. Patient acceptability and psychologic consequences of CT colonography compared with those of colonoscopy: results from a multicenter randomized controlled trial of symptomatic patients. Radiology 2012; 263: 723-731.
163. Young JM, Butow PN, Walsh J et al. Multicenter randomized trial of centralized nurse-led telephone-based care coordination to improve outcomes after surgical resection for colorectal cancer: the CONNECT intervention. J Clin Oncol 2013; 31: 3585-3591.

164. Kennedy RH, Francis EA, Wharton R et al. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol 2014; 32: 1804-1811.
165. Cappello C, Tremolaterra F, Pascariello A et al. A randomised clinical trial (RCT) of a symbiotic mixture in patients with irritable bowel syndrome (IBS): effects on symptoms, colonic transit and quality of life. Int J Colorectal Dis 2013; 28: 349-358.
166. Hart SL, Lee JW, Berian J et al. A randomized controlled trial of anorectal biofeedback for constipation. Int J Colorectal Dis 2012; 27: 459-466.
167. El Miedany Y. Adopting patient-centered care in standard practice: PROMs moving toward disease-specific era. Clin Exp Rheumatol 2014; 32: S-40-46.
168. Dietz de Loos DA, Segboer CL, Gevorgyan A, Fokkens WJ. Disease-specific quality-of-life questionnaires in rhinitis and rhinosinusitis: review and evaluation. Curr Allergy Asthma Rep 2013; 13: 162-170.
169. Sartorio A, Agosti F, De Col A et al. Concurrent comparison of the measurement properties of generic and disease-specific questionnaires in obese inpatients. J Endocrinol Invest 2014; 37: 31-42.
170. Wiebe S, Guyatt G, Weaver B et al. Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol 2003; 56: 52-60.
171. Wong CK, Lam CL, Law WL et al. Condition-specific measure was more responsive than generic measure in colorectal cancer: all but social domains. J Clin Epidemiol 2013; 66: 557-565.
172. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014; 32: 1277-1280.
173. Byrne C, Griffin A, Blazeby J et al. Health-related quality of life as a valid outcome in the treatment of advanced colorectal cancer. Eur J Surg Oncol 2007; 33 Suppl 2: S95-104.
174. Blazeby JM, Fayers P, Conroy T et al. Validation of the European Organization for Research and Treatment of Cancer QLQ-LMC21 questionnaire for assessment of patient-reported outcomes during treatment of colorectal liver metastases. Br J Surg 2009; 96: 291-298.
175. Bhangu A, Ali SM, Brown G et al. Indications and outcome of pelvic exenteration for locally advanced primary and recurrent rectal cancer. Ann Surg 2014; 259: 315-322.
176. Bosman SJ, Vermeer TA, Dudink RL et al. Abdominosacral resection: long-term outcome in 86 patients with locally advanced or locally recurrent rectal cancer. Eur J Surg Oncol 2014; 40: 699-705.
177. Vermaas M, Ferenschild FT, Verhoef C et al. Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. Eur J Surg Oncol 2007; 33: 452-458.
178. Downing A, Morris EJ, Richards M et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol 2015; 33: 616-624.
179. Wiltink LM, Chen TY, Nout RA et al. Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomised trial. Eur J Cancer 2014; 50: 2390-2398.
180. Andersson J, Angenete E, Gellerstedt M et al. Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial. Br J Surg 2013; 100: 941-949.
181. Solomon MJ. Re-exenteration for recurrent rectal cancer. Dis Colon Rectum 2013; 56: 4-5.
182. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. In. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm: 2009.
183. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ 2010; 341: c4587.
184. Bazeley P. Integrative Analysis Strategies for Mixed Data Sources. American Behavioral Scientist 2012; 56: 814-828.

185. Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. Eur J Surg Oncol 2001; 27: 349-353.
186. Zoucas E, Frederiksen S, Lydrup ML et al. Pelvic exenteration for advanced and recurrent malignancy. World J Surg 2010; 34: 2177-2184.
187. You YN, Habiba H, Chang GJ et al. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. Ann Surg Oncol 2011; 18: 989-996.
188. Esnaola NF, Cantor SB, Johnson ML et al. Pain and quality of life after treatment in patients with locally recurrent rectal cancer. J Clin Oncol 2002; 20: 4361-4367.
189. Mannaerts GH, Schijven MP, Hendrikx A et al. Urologic and sexual morbidity following multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Eur J Surg Oncol 2001; 27: 265-272.
190. Mannaerts GH, Rutten HJ, Martijn H et al. Effects on functional outcome after IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2002; 54: 1082-1088.
191. Austin KK, Young JM, Solomon MJ. Quality of life of survivors after pelvic exenteration for rectal cancer. Dis Colon Rectum 2010; 53: 1121-1126.
192. Palmer G, Martling A, Lagergren P et al. Quality of life after potentially curative treatment for locally advanced rectal cancer. Ann Surg Oncol 2008; 15: 3109-3117.
193. Guren MG, Wiig JN, Dueland S et al. Quality of life in patients with urinary diversion after operation for locally advanced rectal cancer. Eur J Surg Oncol 2001; 27: 645-651.
194. Wright FC, Crooks D, Fitch M et al. Qualitative assessment of patient experiences related to extended pelvic resection for rectal cancer. J Surg Oncol 2006; 93: 92-99.
195. Holman FA, Martijnse IS, Traa MJ et al. Dynamic article: vaginal and perineal reconstruction using rectus abdominis myocutaneous flap in surgery for locally advanced rectum carcinoma and locally recurrent rectum carcinoma. Dis Colon Rectum 2013; 56: 175-185.
196. Thaysen HV, Jess P, Rasmussen PC, Laurberg S. Health-related quality of life after surgery for locally advanced primary rectal cancer and recurrent rectal cancer. Colorectal Dis 2012; 14: 14.
197. Vaughan P, Shaw R, Sreekumar R et al. Contribution of surgery and disease subtype to health related quality of life in patients with locally advanced and recurrent colorectal cancer. Br J Surg 2012; 99: 93.
198. Vaughan P SR, Sreekumar R, Bullock M, Knight J, Mirnezami A. Contribution of surgery and disease subtype to health related quality of life in patients with locally advanced and recurrent colorectal cancer. . Br J Surg 2012; 99: 93.
199. Badia X, Muriel C, Gracia A et al. [Validation of the Spanish version of the Brief Pain Inventory in patients with oncological pain]. Med Clin (Barc) 2003; 120: 52-59.
200. Ferenschild FT, Vermaas M, Verhoef C et al. Total pelvic exenteration for primary and recurrent malignancies. World J Surg 2009; 33: 1502-1508.
201. Yamada K, Ishizawa T, Niwa K et al. Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer. Dis Colon Rectum 2002; 45: 1078-1084.
202. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 2002; 324: 1417.
203. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23: 129-138.
204. Cleeland CS, Gonin R, Hatfield AK et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994; 330: 592-596.
205. Yoo HJ, Kim JC, Eremenco S, Han OS. Quality of life in colorectal cancer patients with colectomy and the validation of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), Version 4. J Pain Symptom Manage 2005; 30: 24-32.
206. Rotonda C, Conroy T, Mercier M et al. Validation of the French version of the colorectal-specific quality-of-life questionnaires EORTC QLQ-CR38 and FACT-C. Qual Life Res 2008; 17: 437-445.

207. Law CC, Tak Lam WW, Fu YT et al. Validation of the Chinese version of the EORTC colorectal cancer-specific quality-of-life questionnaire module (QLQ-CR38). J Pain Symptom Manage 2008; 35: 203-213.
208. Tsunoda A, Yasuda N, Nakao K et al. Validation of the Japanese version of EORTC QLQ-CR38. Qual Life Res 2008; 17: 317-322.
209. Whistance RN, Conroy T, Chie W et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009; 45: 3017-3026.
210. Arraras JI, Suarez J, Arias de la Vega F et al. The EORTC Quality of Life questionnaire for patients with colorectal cancer: EORTC QLQ-CR29 validation study for Spanish patients. Clin Transl Oncol 2011; 13: 50-56.
211. Nowak W, Tobiasz-Adamczyk B, Brzyski P et al. Adaptation of quality of life module EORTC QLQ-CR29 for Polish patients with rectal cancer: initial assessment of validity and reliability. Pol Przegl Chir 2011; 83: 502-510.
212. Sprangers MA, Cull A, Groenvold M et al. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC Quality of Life Study Group. Qual Life Res 1998; 7: 291-300.
213. Wells GA, Russell AS, Haraoui B et al. Validity of quality of life measurement tools--from generic to disease-specific. J Rheumatol Suppl 2011; 88: 2-6.
214. Nielsen M, Rasmussen P, Lindegaard J, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. Colorectal Dis 2011.
215. Ike H, Shimada H, Yamaguchi S et al. Outcome of total pelvic exenteration for primary rectal cancer. Dis Colon Rectum 2003; 46: 474-480.
216. Ike H, Shimada H, Ohki S et al. Outcome of total pelvic exenteration for locally recurrent rectal cancer. Hepatogastroenterology 2003; 50: 700-703.
217. Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer. Surg Oncol Clin N Am 2005; 14: 225-238.
218. Yoo HJ, Lim MC, Seo SS et al. Pelvic exenteration for recurrent cervical cancer: ten-year experience at National Cancer Center in Korea. J Gynecol Oncol 2012; 23: 242-250.
219. (CRD). CfRaD. Systematic reviews: CRD's guidance for undertaking reviews in health care. York, UK: CRD; 2009.
220. Higgins J GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]

221. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62: e1-34.
222. Criticial Appraisal Skills Programme (CASP). In.
223. K. H. Chapter 4: Critical appraisal of qualitative research. In: Noyes J, Booth A, Hannes K, Harden A, Harris J, Lewin S, Lockwood C (editors), Supplementary Guidance for Inclusion of Qualitative Research in Cochrane Systematic Reviews of Interventions. Version 1 (updated August 2011). Cochrane Collaboration Qualitative Methods Group, 2011. Available from URL http://cqrmg.cochrane.org/supplemental-handbook-guidance.
224. Hoffe H, Yardley J . Content and thematic analysis. . London, Sage,2004.
225. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs 2008; 62: 107-115.
226. Dempsey GM, Buchsbaum HJ, Morrison J. Psychosocial adjustment to pelvic exenteration. Gynecol Oncol 1975; 3: 325-334.
227. Vera MI. Quality of life following pelvic exenteration. Gynecol Oncol 1981; 12: 355-366.
228. Corney RH, Crowther ME, Everett H et al. Psychosexual dysfunction in women with gynaecological cancer following radical pelvic surgery. Br J Obstet Gynaecol 1993; 100: 73-78.

229. Mirhashemi R, Averette HE, Lambrou N et al. Vaginal reconstruction at the time of pelvic exenteration: a surgical and psychosexual analysis of techniques. Gynecol Oncol 2002; 87: 39-45.
230. Carter J, Chi DS, Abu-Rustum N et al. Brief report: total pelvic exenteration--A retrospective clinical needs assessment. Psychooncology 2004; 13: 125-131.
231. Love US, Sjogren P, Rasmussen P et al. Sexual dysfunction after colpectomy and vaginal reconstruction with a vertical rectus abdominis myocutaneous flap. Dis Colon Rectum 2013; 56: 186-190.
232. Rezk YA, Hurley KE, Carter J et al. A prospective study of quality of life in patients undergoing pelvic exenteration: Interim results. Gynecol Oncol 2012.
233. Guimaraes GC, Baiocchi G, Ferreira FO et al. Palliative pelvic exenteration for patients with gynecological malignancies. Arch Gynecol Obstet 2011; 283: 1107-1112.
234. Forner DM, Lampe B. Ileal conduit and continent ileocecal pouch for patients undergoing pelvic exenteration: comparison of complications and quality of life. Int J Gynecol Cancer 2011; 21: 403-408.
235. Hawighorst-Knapstein S, Fusshoeller C, Franz C et al. The impact of treatment for genital cancer on quality of life and body image--results of a prospective longitudinal 10-year study. Gynecol Oncol 2004; 94: 398-403.
236. Hawighorst S, Schoenefuss G, Fusshoeller C et al. The physician-patient relationship before cancer treatment: a prospective longitudinal study. Gynecol Oncol 2004; 94: 93-97.
237. Hawighorst-Knapstein S, Schonefussrs G, Hoffmann SO, Knapstein PG. Pelvic exenteration: effects of surgery on quality of life and body image--a prospective longitudinal study. Gynecol Oncol 1997; 66: 495-500.
238. Roos EJ, de Graeff A, van Eijkeren MA et al. Quality of life after pelvic exenteration. Gynecol Oncol 2004; 93: 610-614.
239. Woodhouse CR, Plail RO, Schlesinger PE et al. Exenteration as palliation for patients with advanced pelvic malignancy. Br J Urol 1995; 76: 315-320.
240. Brophy PF, Hoffman JP, Eisenberg BL. The role of palliative pelvic exenteration. Am J Surg 1994; 167: 386-390.
241. Gleeson N, Baile W, Roberts WS et al. Surgical and psychosexual outcome following vaginal reconstruction with pelvic exenteration. Eur J Gynaecol Oncol 1994; 15: 89-95.
242. Andersen BL, Hacker NF. Psychosexual adjustment following pelvic exenteration. Obstet Gynecol 1983; 61: 331-338.
243. Ladwig KH, Marten-Mittag B, Formanek B, Dammann G. Gender differences of symptom reporting and medical health care utilization in the German population. Eur J Epidemiol 2000; 16: 511-518.
244. Kroenke K, Spitzer RL. Gender differences in the reporting of physical and somatoform symptoms. Psychosom Med 1998; 60: 150-155.
245. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001; 16: 266-275.
246. Gillen MM, Lefkowitz ES. Gender and racial/ethnic differences in body image development among college students. Body Image 2012; 9: 126-130.
247. El Ansari W, Clausen SV, Mabhala A, Stock C. How do I look? Body image perceptions among university students from England and Denmark. Int J Environ Res Public Health 2010; 7: 583-595.
248. Ahmed K, Kyte D, Keeley T et al. Systematic evaluation of patient-reported outcome (PRO) protocol content and reporting in UK cancer clinical trials: the EPiC study protocol. BMJ Open 2016; 6: e012863.
249. Bylicki O, Gan HK, Joly F et al. Poor patient-reported outcomes reporting according to CONSORT guidelines in randomized clinical trials evaluating systemic cancer therapy. Ann Oncol 2015; 26: 231-237.
250. Kotronoulas G, Kearney N, Maguire R et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and

health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 2014; 32: 1480-1501.
251. Howell D, Molloy S, Wilkinson K et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol 2015; 26: 1846-1858.
252. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 2013; 13: 211.
253. Patrick DL, Burke LB, Gwaltney CJ et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. Value Health 2011; 14: 967-977.
254. Trust SACotMO. Assessing health status and quality-of-life instruments: Attributes and review

criteria. Qual Life Res 2002; 11: 193-205.
255. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002; 11: 193-205.
256. Coons SJ, Gwaltney CJ, Hays RD et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. Value Health 2009; 12: 419-429.
257. Sprangers MA, Cull A, Bjordal K et al. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. Qual Life Res 1993; 2: 287-295.
258. http://groups.eortc.be/qol/sites/default/files/archives/guidelines_for_developing_questionnaire-_final.pdf. In.
259. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: developing best practices based on science and experience. Qual Life Res 2009; 18: 1263-1278.
260. Gimeno-Santos E, Frei A, Dobbels F et al. Validity of instruments to measure physical activity may be questionable due to a lack of conceptual frameworks: a systematic review. Health Qual Life Outcomes 2011; 9: 86.
261. Green J, Willis K, Hughes E et al. Generating best evidence from qualitative research: the role of data analysis. Aust N Z J Public Health 2007; 31: 545-550.
262. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005; 15: 1277-1288.
263. Davidge KM, Eskicioglu C, Lipa J et al. Qualitative assessment of patient experiences following sacrectomy. J Surg Oncol 2010; 101: 447-450.
264. Wright FC, Simunovic M, Coates A, Fitch M. Quality initiative in rectal cancer strategy: a qualitative study of participating surgeons. J Am Coll Surg 2006; 203: 795-802.
265. Harji DP, Griffiths B, McArthur DR, Sagar PM. Current UK Management of Locally Recurrent Rectal Cancer. Colorectal Dis 2012.
266. Gnanasakthy A, Lewis S, Clark M et al. Potential of patient-reported outcomes as nonprimary endpoints in clinical trials. Health Qual Life Outcomes 2013; 11: 83.
267. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003; 1: 79.
268. Coons SJ, Kothari S, Monz BU, Burke LB. The patient-reported outcome (PRO) consortium: filling measurement gaps for PRO end points to support labeling claims. Clin Pharmacol Ther 2011; 90: 743-748.
269. Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. Los Angeles, CA ; London: SAGE,2011.

270. Krueger RA, Casey MA. Focus groups : a practical guide for applied research. London: SAGE,2009.
271. Cooper CP, Jorgensen CM, Merritt TL. Report from the CDC. Telephone focus groups: an emerging method in public health research. J Womens Health (Larchmt) 2003; 12: 945-951.
272. Frazier LM, Miller VA, Horbelt DV et al. Comparison of focus groups on cancer and employment conducted face to face or by telephone. Qual Health Res 2010; 20: 617-627.
273. Brink HI. Validity and reliability in qualitative research. Curationis 1993; 16: 35-38.
274. Mokkink LB, Terwee CB, Patrick DL et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol 2010; 63: 737-745.
275. Mokkink LB, Terwee CB, Knol DL et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol 2010; 10: 22.
276. Mokkink LB, Terwee CB, Patrick DL et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010; 19: 539-549.
277. Greimel E, Bottomley A, Cull A et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 2003; 39: 1402-1408.
278. Cella D. Manual of the functional assessment of chronic illness therapy (FACIT) measurement system. .1997.
279. Wild D, Eremenco S, Mear I et al. Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. Value Health 2009; 12: 430-440.
280. Wild D, Grove A, Martin M et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 2005; 8: 94-104.
281. Rothman M, Burke L, Erickson P et al. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. Value Health 2009; 12: 1075-1083.
282. Reeve BB, Wyrwich KW, Wu AW et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013.
283. Reeve BB, Wyrwich KW, Wu AW et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013; 22: 1889-1905.
284. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.
285. Whistance RN, Conroy T, Chie W et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009; 45: 3017-3026.
286. Cella DF, Tulsky DS, Gray G et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993; 11: 570-579.
287. Grant M, Ferrell B, Dean G et al. Revision and psychometric testing of the City of Hope Quality of Life-Ostomy Questionnaire. Qual Life Res 2004; 13: 1445-1457.
288. Prieto L, Thorsen H, Juul K. Development and validation of a quality of life questionnaire for patients with colostomy or ileostomy. Health Qual Life Outcomes 2005; 3: 62.

289. Baxter NN, Novotny PJ, Jacobson T et al. A stoma quality of life scale. Dis Colon Rectum 2006; 49: 205-212.
290. Temple LK, Bacik J, Savatta SG et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. Dis Colon Rectum 2005; 48: 1353-1365.
291. Snyder CF, Watson ME, Jackson JD et al. Patient-reported outcome instrument selection: designing a measurement strategy. Value Health 2007; 10 Suppl 2: S76-85.
292. Patrick DL, Burke LB, Gwaltney CJ et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding. Value Health 2011; 14: 978-988.
293. http://groups.eortc.be/qol/sites/default/files/archives/guidelines_for_developing_questionnaire-_final.pdf. . In.
294. http://groups.eortc.be/qol/item-bank. In.
295. http://www.proqolid.org. In.
296. Mullin PA, Lohr KN, Bresnahan BW, McNulty P. Applying cognitive design principles to formatting HRQOL instruments. Qual Life Res 2000; 9: 13-27.
297. Dillman D, Sinclair MD, Clark JR. Effects of questionnaire length, respondent-friendly design, and a difficult question on response rates for occupant-addressed Census mail surveys. Public Opin Quart 1993; 57: 289-304.
298. McColl E, Jacoby A, Thomas L et al. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. Health Technol Assess 2001; 5: 1-256.
299. Slattery EL, Voelker CC, Nussenbaum B et al. A practical guide to surveys and questionnaires. Otolaryngol Head Neck Surg 2011; 144: 831-837.
300. Boynton PM, Greenhalgh T. Selecting, designing, and developing your questionnaire. BMJ 2004; 328: 1312-1315.
301. Leung WC. How to design a questionnaire. BMJ Student 2001; 9: 187-189.
302. Calderon JL, Fleming E, Gannon MR et al. Applying an expanded set of cognitive design principles to formatting the Kidney Early Evaluation Program (KEEP) longitudinal survey. Am J Kidney Dis 2008; 51: S83-92.
303. Bissett A. Designing a questionnaire: Send a personal covering letter. . BMJ 1994; 308: 202-203.
304. Brinkman W. Design of a Questionnaire Instrument, Handbook of Mobile Technology Research Methods. Nova Publisher,2009.
305. Schriesheim CA DA. Item presentations as an influence on questionnaire validity: A field experiment. Educational Psychol Measur 1980; 40: 175-182.
306. Turner RR, Quittner AL, Parasuraman BM et al. Patient-reported outcomes: instrument development and selection issues. Value Health 2007; 10 Suppl 2: S86-93.
307. Rattray J, Jones MC. Essential elements of questionnaire design and development. J Clin Nurs 2007; 16: 234-243.
308. McColl E, Meadows K, Barofsky I. Cognitive aspects of survey methodology and quality of life assessment. Qual Life Res 2003; 12: 217-218.
309. Barofsky I, Meadows K, McColl E. Cognitive aspects of survey methodology and quality of life assessment: summary of meeting. Qual Life Res 2003; 12: 281-282.
310. Tourangeau R, Rips LJ, Rasinski KA. The psychology of survey response. Cambridge: Cambridge University Press,2000.
311. Barofsky I. Cognitive approaches to summary measurement: its application to the measurement of diversity in health-related quality of life assessments. Qual Life Res 2003; 12: 251-260.

312. Drennan J. Cognitive interviewing: verbal data in the design and pretesting of questionnaires. Journal of Advanced Nursing 2002; 42: 57-63.
313. Czaja R. Questionnaire pretesting comes of age. Marketing Bulletin 1998; 9: 52-56.
314. Collins D. Pretesting survey instruments: an overview of cognitive methods. Qual Life Res 2003; 12: 229-238.
315. Willis G, Lesser JT. Question Appraisal System: QAS 99. National Cancer Institute 1999.
316. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993; 2: 451-459.
317. Lee J. Conducting Cognitive Interviews in Cross-National Settings. Assessment 2012; 21: 227-240.
318. Hui CH, Triandis, H.C. Measurement in cross-cultural psychology: A review and comparison of strategies. . Journal of Cross-Cultural Psychology 1985; 16: 131-152.
319. Banner DJ, Albarrran JW. Computer-assisted qualitative data analysis software: a review. Can J Cardiovasc Nurs 2009; 19: 24-31.
320. McLafferty E, Farley AH. Analysing qualitative research data using computer software. Nurs Times 2006; 102: 34-36.
321. Beaton J, Carey S, Solomon MJ et al. Preoperative body mass index, 30-day postoperative morbidity, length of stay and quality of life in patients undergoing pelvic exenteration surgery for recurrent and locally-advanced rectal cancer. Ann Coloproctol 2014; 30: 83-87.
322. Young JM, Badgery-Parker T, Masya LM et al. Quality of life and other patient-reported outcomes following exenteration for pelvic malignancy. Br J Surg 2014; 101: 277-287.
323. Revicki DA, Gnanasakthy A, Weinfurt K. Documenting the rationale and psychometric characteristics of patient reported outcomes for labeling and promotional claims: the PRO Evidence Dossier. Qual Life Res 2007; 16: 717-723.
324. Thaysen HV JP, Rasmussen PC, Laurberg S. Health-related quality of life after surgery for locally advanced primary rectal cancer and recurrent rectal cancer. Colorectal Dis 14: 14.
325. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994; 32: 40-66.
326. Gandek B, Ware JE, Jr., Aaronson NK et al. Tests of data quality, scaling assumptions, and reliability of the SF-36 in eleven countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51: 1149-1158.
327. Ware JE SK, Kosinski M, Gandek B. . SF-36 Health Survey Manual and Interpretation Guide. In Boston MNEMC, The Health Institute; (ed). 1993.
328. Fairclough DL, Cella DF. Functional Assessment of Cancer Therapy (FACT-G): non-response to individual questions. Qual Life Res 1996; 5: 321-329.
329. Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. Stat Methods Med Res 2014; 23: 440-459.
330. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull 1959; 56: 81-105.
331. Stewart AL HR, Ware JE. . Methods of constructing health measures. In: Stewart AL, Ware JE, Eds. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. London: Duke University Press,1992.
332. Hays RD HT. Beyond internal consistency reliability:

Rationale and user's guide for Multitrait Analysis Program on

the microcomputer. Behav Res Methods Instruments Computers 1990; 22: 167-175.
333. Ware JE HW, Gandek B, Rogers BW, Reese PR. . MAP-R

for Windows: Multitrait/Multi-Item Scale Analysis Software. Boston, MA: Health Assessment Lab 1997.

334. Yurdugül H. Minimum sample size for Cronbach's coefficient alpha: A Monte-Carlo study. Hacettepe Üniversitesi Eğitim Fakültesi Dergisi 2008; 35: 397-405.
335. Guadagnoli. E VWF. Relation to sample size to the stability of component patterns. Psychol Bull 1998; 103: 265-275.
336. Muller R, Buttner P. A critical discussion of intraclass correlation coefficients. Stat Med 1994; 13: 2465-2476.
337. Costello A, Osbourne JW. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Practical Assessment Research & Evaluation 2005; 10.
338. Hogarthy. K HC, Kromrey JD, Ferron JM, Mumford KR. The quality of factor solutions in exploratory factor analysis: the influence of sample size, communality and overdetermination. Educational and Psychological Measurement 2005; 65: 202 - 226.
339. MacCallum RC, Widaman, K.F, Zhang, S.B, Hong, S. Sample Size in Factor Analysis. Psychol Methods 1999; 4: 84 - 99.
340. Al-Shahi Salman R, Brock TM, Dennis MS et al. Research governance impediments to clinical trials: a retrospective survey. J R Soc Med 2007; 100: 101-104.
341. Jonker L, Cox, D, Marsahll G. Considerations, clues and challenges: Gaining Ethical and Trust research approval when using the NHS as a research setting. Radiography 2011; 17: 260 - 264.
342. Kearney A, McKay A, Hickey H et al. Opening research sites in multicentre clinical trials within the UK: a detailed analysis of delays. BMJ Open 2014; 4: e005874.
343. Cook D, McDonald E, Smith O et al. Co-enrollment of critically ill patients into multiple studies: patterns, predictors and consequences. Crit Care 2013; 17: R1.
344. Myles PS, Williamson E, Oakley J, Forbes A. Ethical and scientific considerations for patient enrollment into concurrent clinical trials. Trials 2014; 15: 470.
345. Corner J. Is there a research paradigm for palliative care? Palliat Med 1996; 10: 201-208.
346. Hanson LC, Bull J, Wessell K et al. Strategies to support recruitment of patients with life-limiting illness for research: the Palliative Care Research Cooperative Group. J Pain Symptom Manage 2014; 48: 1021-1030.
347. Basch E, Bennett AV. Patient-reported outcomes in clinical trials of rare diseases. J Gen Intern Med 2014; 29 Suppl 3: S801-803.
348. Billingham L, Malottki K, Steven N. Research methods to change clinical practice for patients with rare cancers. Lancet Oncol 2016; 17: e70-80.
349. Griggs RC, Batshaw M, Dunkle M et al. Clinical research for rare disease: opportunities, challenges, and solutions. Mol Genet Metab 2009; 96: 20-26.
350. Bolignano D, Pisano A. Good-quality research in rare diseases: trials and tribulations. Pediatr Nephrol 2016; 31: 2017-2023.
351. Barra M, Simonsen TB, Dahl FA. Pre-contact by telephone increases response rates to postal questionnaires in a population of stroke patients: an open ended randomized controlled trial. BMC Health Serv Res 2016; 16: 506.
352. Edwards P, Roberts I, Clarke M et al. Increasing response rates to postal questionnaires: systematic review. BMJ 2002; 324: 1183.
353. Sahlqvist S, Song Y, Bull F et al. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: randomised controlled trial. BMC Med Res Methodol 2011; 11: 62.
354. Sharma A, Walker LG, Monson JR. Baseline quality of life factors predict long term survival after elective resection for colorectal cancer. Int J Surg Oncol 2013; 2013: 269510.
355. Horevoorts NJ, Vissers PA, Mols F et al. Response rates for patient-reported outcomes using web-based versus paper questionnaires: comparison of two invitational methods in older colorectal cancer patients. J Med Internet Res 2015; 17: e111.

356. Diouf M, Chibaudel B, Filleron T et al. Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study. Health Qual Life Outcomes 2014; 12: 69.
357. Braun DP, Gupta D, Grutsch JF, Staren ED. Can changes in health related quality of life scores predict survival in stages III and IV colorectal cancer? Health Qual Life Outcomes 2011; 9: 62.
358. Anthoine E, Moret L, Regnault A et al. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health Qual Life Outcomes 2014; 12: 176.
359. Comfrey A. A first course in Factor Analysis. NY: Academic Press NY,1973.
360. Guilford JP. Psychometric methods. New York ; London: McGraw-Hill,1954.
361. Gorsuch RL. Factor analysis. Philadelphia ; London: Saunders,1974.
362. de Winter. JCF DD, Wieringa. PA, . Exploratory Factor Analysis With Small Sample Sizes. Multivariate Behavioural Research 2009; 44: 147 - 181.
363. Nunnally JC, Bernstein IH. Psychometric theory. New York: McGraw-Hill,1994.
364. Iacobucci D, Duhachek A. Advancing Alpha: Measuring Reliability with Confidence. Journal of Consumer Psychology 2003; 13: 478 - 487.
365. Charter RA. Sample Size Requirements for Precise Estimates of Reliability, Generalizability, and Validity Coefficients. Journal of Clinical and Experimental Neuropsychology 1999; 21: 559-566.
366. DeVellis RF. Classical test theory. Med Care 2006; 44: S50-59.
367. Cappelleri JC, Jason Lundy J, Hays RD. Overview of classical test theory and item response theory for the quantitative assessment of items in developing patient-reported outcomes measures. Clin Ther 2014; 36: 648-662.
368. Petrillo J, Cano SJ, McLeod LD, Coon CD. Using classical test theory, item response theory, and Rasch measurement theory to evaluate patient-reported outcome measures: a comparison of worked examples. Value Health 2015; 18: 25-34.
369. Rothman ML, Beltran P, Cappelleri JC et al. Patient-reported outcomes: conceptual issues. Value Health 2007; 10 Suppl 2: S66-75.
370. L. MD. The focus group guide book. London: Sage Publications,1998.
371. Sim J. Collecting and analysing qualitative data: issues raised by the focus group. J Adv Nurs 1998; 28: 345-352.
372. Ahmed R, McCaffery KJ, Aslani P. Development and validation of a question prompt list for parents of children with attention-deficit/hyperactivity disorder: a Delphi study. Health Expect 2016; 19: 234-252.
373. Murphy M, Hollinghurst S, Salisbury C. Agreeing the content of a patient-reported outcome measure for primary care: a Delphi consensus study. Health Expect 2016.
374. Rothgeb J, Willis G, Forsyth B. Questionnaire pretesting methods: Do different techniques and different organizations produce similar results? Bulletin de méthodologie sociologique 2007; 96: 5-31.
375. Presser S, Blair J. Survey pretesting: Do different methods produce different results. Sociological methodology 1994; 24: 73-104.
376. Gorecki C, Lamping DL, Nixon J et al. Applying mixed methods to pretest the Pressure Ulcer Quality of Life (PU-QOL) instrument. Qual Life Res 2012; 21: 441-451.
377. Tadic V, Cooper A, Cumberland P et al. Measuring the Quality of Life of Visually Impaired Children: First Stage Psychometric Evaluation of the Novel VQoL_CYP Instrument. PLoS One 2016; 11: e0146225.
378. Pusic AL, Klassen AF, Scott AM et al. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. Plast Reconstr Surg 2009; 124: 345-353.
379. Marfeo EE, Ni P, Haley SM et al. Scale refinement and initial evaluation of a behavioral health function measurement tool for work disability evaluation. Arch Phys Med Rehabil 2013; 94: 1679-1686.

380. Cano SJ, Klassen AF, Scott A et al. Reply: The Rasch model: "Litmus Test" de rigueur for rating scales? Plast Reconstr Surg 2013; 131: 286e-288e.
381. Nguyen TH, Han HR, Kim MT, Chan KS. An introduction to item response theory for patient-reported outcome measurement. Patient 2014; 7: 23-35.
382. Gagne JJ, Thompson L, O'Keefe K, Kesselheim AS. Innovative research methods for studying treatments for rare diseases: methodological review. BMJ 2014; 349: g6802.
383. Chow SC, Chang M. Adaptive design methods in clinical trials - a review. Orphanet J Rare Dis 2008; 3: 11.
384. Gurka MJ, Coffey CS, Gurka KK. Internal pilots for observational studies. Biom J 2010; 52: 590-603.
385. Schmied W, Barnick S, Heimann D et al. [Quality of life or life expectancy? Criteria and sources of information in the decision-making of patients undergoing aortic valve surgery]. Z Psychosom Med Psychother 2015; 61: 224-237.
386. Reyes ME, Ye Y, Zhou Y et al. Predictors of health-related quality of life and association with survival may identify colorectal cancer patients at high risk of poor prognosis. Qual Life Res 2017; 26: 319-330.
387. Pompili C, Salati M, Refai M et al. Preoperative quality of life predicts survival following pulmonary resection in stage I non-small-cell lung cancer. Eur J Cardiothorac Surg 2013; 43: 905-910.
388. Suh SY, Leblanc TW, Shelby RA et al. Longitudinal patient-reported performance status assessment in the cancer clinic is feasible and prognostic. J Oncol Pract 2011; 7: 374-381.
389. Snyder CF, Blackford AL, Wolff AC et al. Feasibility and value of PatientViewpoint: a web system for patient-reported outcomes assessment in clinical practice. Psychooncology 2013; 22: 895-901.
390. Berry DL, Blumenstein BA, Halpenny B et al. Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. J Clin Oncol 2011; 29: 1029-1035.
391. Braeken AP, Kempen GI, Eekers D et al. The usefulness and feasibility of a screening instrument to identify psychosocial problems in patients receiving curative radiotherapy: a process evaluation. BMC Cancer 2011; 11: 479.
392. Thewes B, Butow P, Stuart-Harris R, Greater Southern Area Health Service Screening Collaborative G. Does routine psychological screening of newly diagnosed rural cancer patients lead to better patient outcomes? Results of a pilot study. Aust J Rural Health 2009; 17: 298-304.
393. Dobrozsi S, Panepinto J. Patient-reported outcomes in clinical practice. Hematology Am Soc Hematol Educ Program 2015; 2015: 501-506.
394. Ganz PA, Greendale GA, Petersen L et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst 2000; 92: 1054-1064.
395. Black N, Varagunam M, Hutchings A. Influence of surgical rate on patients' reported clinical need and outcomes in English NHS. J Public Health (Oxf) 2014; 36: 497-503.
396. Black N, Burke L, Forrest CB et al. Patient-reported outcomes: pathways to better health, better services, and better societies. Qual Life Res 2016; 25: 1103-1112.
397. Van Der Wees PJ, Nijhuis-Van Der Sanden MW, Ayanian JZ et al. Integrating the use of patient-reported outcomes for both clinical practice and performance measurement: views of experts from 3 countries. Milbank Q 2014; 92: 754-775.
398. Forward FYFVAWCCOTtS. In.
399. Terwee CB, Dekker FW, Wiersinga WM et al. On assessing responsiveness of health-related quality of life instruments: guidelines for instrument evaluation. Qual Life Res 2003; 12: 349-362.
400. Rasch G. Probabilistic models for some intelligence and attainment tests. Copenhagen: [s.n.],1960.
401. Andrich D. Rasch models for measurement. Newbury Park, Calif. ; London: Sage,1988.
402. Cella D, Chang CH. A discussion of item response theory and its applications in health status assessment. Med Care 2000; 38: II66-72.

403. Chang CH, Reeve BB. Item response theory and its applications to patient-reported outcomes measurement. Eval Health Prof 2005; 28: 264-282.
404. Hobart J, Cano S. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. Health Technol Assess 2009; 13: iii, ix-x, 1-177.
405. Linacre JM. Optimizing rating scale category effectiveness. J Appl Meas 2002; 3: 85-106.
406. Chen YF, Madan J, Welton N et al. Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: a systematic review and network meta-analysis. Health Technol Assess 2012; 16: 1-205, iii-v.
407. Hui CY, Walton R, McKinstry B et al. The use of mobile applications to support self-management for people with asthma: a systematic review of controlled studies to identify features associated with clinical effectiveness and adherence. J Am Med Inform Assoc 2016.
408. Ashley L, Jones H, Thomas J et al. Integrating patient reported outcomes with clinical cancer registry data: a feasibility study of the electronic Patient-Reported Outcomes From Cancer Survivors (ePOCS) system. J Med Internet Res 2013; 15: e230.
409. Rothman M, Gnanaskathy A, Wicks P, Papadopoulos EJ. Can we use social media to support content validity of patient-reported outcome instruments in medical product development? Value Health 2015; 18: 1-4.
410. Chen M, Mangubat E, Ouyang B. Patient-reported outcome measures for patients with cerebral aneurysms acquired via social media: data from a large nationwide sample. J Neurointerv Surg 2016; 8: 42-46.
411. Williamson PR, Altman DG, Bagley H et al. The COMET Handbook: version 1.0. Trials 2017; 18: 280.
412. Whistance RN, Forsythe RO, McNair AG et al. A systematic review of outcome reporting in colorectal cancer surgery. Colorectal Dis 2013; 15: e548-560.
413. McNair AG, Whistance RN, Forsythe RO et al. Synthesis and summary of patient-reported outcome measures to inform the development of a core outcome set in colorectal cancer surgery. Colorectal Dis 2015; 17: O217-229.
414. McNair AG, Whistance RN, Forsythe RO et al. Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. PLoS Med 2016; 13: e1002071.

Appendices

Appendix 1 – Search Strategy for HrQoL in LRRC

Free Text Search Terms

Locally

Recurrent

Rectal

Quality

Life

Quality of life

Symptom prevention and control

Questionnaires

Health Related

Physical

Distress

Psychological

Psychosocial

MeSH Terms

Rectal neoplasms

Quality of Life

Questionnaires

Health

Physical examination

Search Strategy

1. ‘Locally’ (All Fields) and ‘Recurrent’ (All fields) and ‘Rectal Neoplasm’ (MeSH term) or Rectal (All fields)
2. ‘Quality of Life’ (MeSH Term) OR (‘quality’ (All Fields) and ‘life’ (All Fields) OR ‘quality of life’ (All Fields)

3. ‘Health’ (MeSH Terms) OR ‘health’ (All Fields) AND related (All Fields) AND ‘Quality of Life’ (MeSH Terms) OR ‘quality’ (All Fields) AND ‘life’ (All Fields) OR ‘Quality of Life’ (All Fields)
4. ‘Symptom’ (All Fields) AND ‘prevention and control’ (Subheading)
5. ‘Questionnaires’ (MeSH Terms) OR ‘Questionnaires’ (All Fields)
6. ‘Physical Examination’ (MeSH Terms) OR ‘Physical’ (All Fields) AND ‘Examination’ (All Fields) OR ‘Physical Examination’ (All Fields) OR ‘Physical’ (All Fields) AND ‘distress’ (All Fields).
7. ‘Psychological’ (All Fields) AND ‘distress’ (All Fields)
8. ‘Psychosocial’ (All Fields) AND ‘distress’ (All Fields)

Conference Proceedings

Association of Surgeons of Great Britain and Ireland 2000 -2012

Association of Coloproctologists of Great Britain and Ireland 2000 -2012

European Society of Coloproctology 2007-2012

Internet search of web content relating to LRRC self-help and focus group:

- www.macmilian.org
- http://cancerchat.cancerresearchuk.org
- www.beatingbowelcancer.org

Appendix 2 – Topic Guide For Phase I: Focus Groups

LRRC-QoL PROJECT

Topic Guide for Focus Group for the Development of a Conceptual Framework

1. **Welcome**
    a. Introduction
    b. Ground rules including confidentiality, mutual respect and voluntary withdrawal of participation at any time
    c. Participant Introductions

2. **Focus Group Interview**
    Opening Statements
    a. Tell me about your initial experiences of LRRC when you were first diagnosed
    b. Tell me about your experiences of your treatment of LRRC
    c. Tell me about your feelings and experiences following the treatment of LRRC

    For each phase of the management and treatment of LRRC the following key issues will be touched upon.

    i. Symptoms experienced
        1. Pain
        2. Gastrointestinal symptoms
        3. Genitourinary symptoms
        4. Sexual symptoms
    ii. How the diagnosis was obtained
    iii. Communication with health care professionals
    iv. Psychological impact
    v. Impact on relationships/finances/work
    vi. Sexual impact

    Cognitive probes will be used to further explore the themes and issues raised by the patients.

    Example cognitive probes:

    - **Pain**
      Where is the location of the pain?
      Which words would you use to describe the pain?
      When do you experience pain? What time of day?
      How often do you experience pain?
      How does pain affect your life and relationships?

    - **Diagnosis obtained**
      How were you diagnosed with LRRC?
      Did you have any symptoms? What were they?
      How did the diagnosis impact your life?
      What information did you receive about your disease from your doctor?

3. **Debrief**
    At the end of the focus group:
    - Debrief the patient
    - Explain their role in the development of LRRC-QoL Tool
    - Thank the patients for their time and help
    - Provide them the opportunity to ask further questions and/or comment

Appendix 3 Topic Guide for Semi-Structured Interviews with Expert Panel for the Development of a Conceptual Framework

LRRC-QoL PROJECT

1. Background

Explanation of background to the study and the development of preliminary conceptual framework to LRRC-QoL questionnaire.

2. Semi-structured Interview Guide

For each domain:

1) Do you think the items in this domain are relevant to patients with LRRC and should be included in the questionnaire?

2) What factors do you think influence the items in this domain?

3) Are there any relevant items that we have left out of this domain?

Overview:

1) Overall, do you think all the domains reflect the experiences of patients with LRRC.
    a. If no, which ones? And how so?

2) Are there any domains which you think might be relevant that have not been included?
    a. If yes, what are they?

3) Overall, do you think the proposed conceptual framework encompasses all issues relevant to patients with LRRC?

3. Additional comments and close of interview

Appendix 4 Provisional Item Pool for LRRC-QoL

1. Have you had abdominal pain?
2. Have you had pain in your lower back and/or pelvis?
3. Have you had pain your back?
4. Have you had pain in your buttocks/anal area/rectum?
5. Have you had pain in your lower back?
6. Has pain interfered with your daily activities?
7. Have you been tired?
8. Have you lacked energy?
9. Have you had irritation or soreness in your vagina or vulva?
10. Have you had any abnormal discharge or bleeding from your vagina?
11. Has your vagina felt short and/or tight?
12. Have you had pain or a burning feeling when passing water/urinating?
13. Have you had any unintentional release (leakage) of urine?
14. Have you had pain when you urinated?
15. Did you have problems caring for your urostomy?
16. Have you felt embarrassed because of your urostomy?
17. Have you have been dependent on others for caring for your urostomy?
18. Have you been troubled by passing wind/gas/flatulence?
19. Have you had any abnormal bleeding or discharge from you rectum?
20. Have you felt embarrassed because of your stoma?
21. Have you had any problems caring for your stoma?
22. Have you had any tingling or numbness in your feet or legs?
23. Have you had any weakness of both legs?
24. Have you worried about loss of mobility because of your illness?
25. Have you had pain during sexual intercourse or other sexual activity?
26. Have you had pain or discomfort during intercourse?
27. Have you felt less interest in sex?
28. Have you felt less sexual enjoyment?
29. For men only: Did you have difficulty gaining or maintaining an erection?
30. For men only: Did you have ejaculation problems (e.g. dry ejaculation)?
31. Have you felt uncomfortable about being sexually intimate?
32. Have you felt depressed?
33. Have you felt anxious?
34. Have you felt angry?
35. Have you felt less confident?
36. Do you feel dependent on others?
37. Have you worried about becoming dependent on others because of your illness?
38. Do you think others perception of you has changed following your medical diagnosis and treatment?
39. Have you felt physically less attractive as a result of your disease or treatment?
40. Have you been dissatisfied with your body?
41. Has your physical condition or medical treatment interfered with your work (occupational) activities?
42. Has your physical condition or medical treatment interfered with your social activities?
43. Has your physical condition or medical treatment interfered with your family life?
44. Have you been limited in doing either your work or daily activities?
45. Have you been limited in pursuing your hobbies or other leisure time activities?
46. Have you had to modify your daily activities because of your illness?
47. Has your physical condition or medical treatment caused you financial difficulties?
48. Do you worry about the results of examinations and tests?
49. Do you worry about new symptoms?

50. Do you worry about possible future treatments?
51. Have you been worried about your health in the future?
52. Have you felt uncertain about the future?
53. Have you felt you've had setbacks in your condition?
54. Do you feel hopeful about your future?
55. Have you felt isolated from those close to you (e.g. family, friends)?
56. Were you satisfied with the information the healthcare professionals gave you about your illness?
57. Were you satisfied with the information the healthcare professionals gave you about your medical tests?
58. Were you satisfied with the information the healthcare professionals gave you about your treatment?
59. Are you satisfied with the treatment and medical follow up provided?
60. Are you satisfied with the diagnosis, treatment and medial follow up provided?
61. Do you expect the treatment to be curative?
62. Are you satisfied with your length of recovery?
63. Were you satisfied with the knowledge and experience of your doctors?
64. Were you satisfied with the waiting times for obtaining results of medical tests?
65. Were you satisfied with the speed of implementing medical tests and/or treatments?
66. Were you satisfied with the frequency of consultations?

Appendix 5: Revised Item Pool

1. Have you had abdominal pain?
2. Have you had pain in your lower back and/or pelvis?
3. Have you had pain in your buttocks/anal area/rectum?
4. Has pain interfered with your daily activities?
5. Have you been tired?
6. Have you lacked energy?
7. Have you had irritation or soreness in your vagina or vulva?
8. Have you had any abnormal discharge or bleeding from your vagina?
9. Have you had pain or a burning feeling when passing water/urinating?
10. Have you had any unintentional release (leakage) of urine?
11. Did you have problems caring for your urostomy?
12. Have you felt embarrassed because of your urostomy?
13. Have you have been dependent on others for caring for your urostomy?
14. Have you had any abnormal bleeding or discharge from you rectum?
15. Have you felt embarrassed because of your stoma?
16. Have you had any problems caring for your stoma?
17. Have you had any tingling or numbness in your feet or legs?
18. Have you had any weakness of both legs?
19. Have you worried about loss of mobility because of your illness?
20. Have you had pain during sexual intercourse or other sexual activity?
21. Have you felt less interest in sex?
22. For men only: Did you have difficulty gaining or maintaining an erection?
23. For men only: Did you have ejaculation problems (e.g. dry ejaculation)?
24. Have you felt depressed?
25. Have you felt anxious?
26. Have you worried about becoming dependent on others because of your illness?
27. Do you think others perception of you has changed following your medical diagnosis and treatment?
28. Have you felt physically less attractive as a result of your disease or treatment?
29. Has your physical condition or medical treatment interfered with your work (occupational) activities?
30. Has your physical condition or medical treatment interfered with your social activities?
31. Has your physical condition or medical treatment interfered with your family life?
32. Has your physical condition or medical treatment caused you financial difficulties?
33. Do you worry about the results of examinations and tests?
34. Do you worry about possible future treatments?
35. Have you been worried about your health in the future?
36. Have you felt uncertain about the future?
37. Were you satisfied with the information the healthcare professionals gave you about your illness?
38. Were you satisfied with the information the healthcare professionals gave you about your treatment?
39. Are you satisfied with the diagnosis, treatment and medial follow up provided?
40. Are you satisfied with your length of recovery?
41. Were you satisfied with the knowledge and experience of your doctors?
42. Were you satisfied with the speed of implementing medical tests and/or treatments?
43. Were you satisfied with the frequency of consultations

Appendix 6: Preliminary Generic LRRC-QoL

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.

Symptoms

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
4. Have you had any abnormal bleeding or discharge from your rectum?.....	1	2	3	4
5. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
6. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?.....	1	2	3	4
9. Have you had any weakness of both legs?.....	1	2	3	4
10. Have you worried about loss of mobility because of your illness?.....	1	2	3	4
11. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4

12. Do you have a urostomy?

Yes...Please go to Question 13
No....Please go to Question 16

13. Did you have problems caring for your urostomy?.....	1	2	3	4
14. Have you felt embarrassed because of your urostomy?.	1	2	3	4
15. Have you have been dependent on others for caring for your urostomy?.....	1	2	3	4

16. Do you have a stoma?

Yes...Please go to Question 17
No....Please go to Question 19

17. Have you felt embarrassed because of your stoma?.....	1	2	3	4
18. Have you had any problems caring for your stoma?.....	1	2	3	4

Psychological Impact

During the past week:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
19. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4
20. Do you think others perception of you has changed following your medical diagnosis and treatment?.....	1	2	3	4
21. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Role Function

During the past week:

	Not at all	A little	Quite a Bit	Very much
22. Has your physical condition or medical treatment interfered with your work (occupational) activities?....	1	2	3	4
23. Has your physical condition or medical treatment interfered with your work (household) activities?.....	1	2	3	4

Sexual Function

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
24. Are you sexually active? Yes...Please go to Question 25 No....Please go to Question 29				
25. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
26. Have you felt less interest in sex?.....	1	2	3	4
27. **For men only**: Did you have difficulty gaining or maintaining an erection?.....	1	2	3	4
28. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
29. Do you worry about the results of examinations and tests?.....	1	2	3	4
30. Do you worry about possible future treatments?.....	1	2	3	4
31. Have you been worried about your health in the future?.....	1	2	3	4

32. Have you felt uncertain about the future?.....	1	2	3	4

Healthcare Services

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
33. Were you satisfied with the information the healthcare professionals gave you about your illness?.....	1	2	3	4
34. Were you satisfied with the information the healthcare professionals gave you about your treatment?.....	1	2	3	4
35. Are you satisfied with the diagnosis, treatment and medial follow up provided?.....	1	2	3	4
36. Are you satisfied with your length of recovery?.....	1	2	3	4
37. Were you satisfied with the knowledge and experience of your doctors?.....	1	2	3	4
38. Were you satisfied with the speed of implementing medical tests and/or treatments?.....	1	2	3	4
39. Were you satisfied with the frequency of consultations?.....	1	2	3	4

Appendix 7 Topic Guide for Cognitive Interviews for the Pre-testing

1. **Welcome**

    a. Introduction
    b. Instructions

2. **Cognitive Interview – Audio recorded**

The interviewer will read out the question to the participant and utilising the principles of the think-aloud technique ask the participant to vocalise their initial responses and thoughts to the question.

Once the participant has completed the initial think-aloud phase, cognitive probes will be used to further explore each question.

Example cognitive probes:

- **Pain in lower back and/or pelvis**
  What do you understand by the term lower back and/or pelvis pain?
  What does that mean to you?
  Are there any other phrases you would use to describe it?
  Is this question clear?
  Is this question easy to understand?
  Was is easy to choose an answer?

- **Have you had any unintentional release (leakage) of urine?**
  What do you understand by the term unintentional release?
  What do you understand by the term leakage?
  What does that mean to you?
  Are there any other phrases you would use to describe this?
  Is this question clear?
  Is this question easy to understand?
  Was it easy to choose an answer?

3. **Debrief**

Debriefing questions regarding the questionnaire.

- *Instructions*

Are the instructions to the questionnaire clear?

- *Recall*

Is the recall period too long/ too short/ just right?

- *Response Options*

  Are the response options clear?

  Are the response options easy to choose?

- *Content coverage*

  Do the questions cover all aspects of HrQoL issues relevant to LRRC?

- *Format*

  Is the format easy to follow?

  Are the skip questions easy to follow and understand?

- *Length*

  Is the questionnaire too long or too short?

  What did you think of the amount of time it took to complete the questionnaire?

- Debrief the patient
- Explain their role in the development of LRRC-QoL Tool
- Thank the patients for their time and help
- Provide them the opportunity to ask further questions and/or comments

Appendix 8: Preliminary LRRC-QoL British version 2

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.

Symptoms **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
4. Have you had any abnormal bleeding or discharge from your rectum?.....	1	2	3	4
5. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
6. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?.....	1	2	3	4
9. Have you had any weakness of both legs?.....	1	2	3	4
10. Have you worried about loss of mobility because of your illness?.....	1	2	3	4
11. Have you had any tingling or numbness in your feet or legs?....	1	2	3	4
12. Have you had pain or discharge from your wound?.....	1	2	3	4

13. Do you have a urostomy?

Yes...Please go to Question 14
No....Please go to Question 17

14. Did you have problems caring for your urostomy?.....	1	2	3	4
15. Have you felt embarrassed because of your urostomy?.....	1	2	3	4
16. Have you have been dependent on others for caring for your urostomy?.....	1	2	3	4

17. Do you have a stoma?

Yes...Please go to Question 18
No....Please go to Question 20

18. Have you felt embarrassed because of your stoma?.....	1	2	3	4
19. Have you had any problems caring for your stoma?.....	1	2	3	4

Psychological Impact

During the past week:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
20. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4
21. Do you think others perception of you has changed following your medical diagnosis and treatment?.....	1	2	3	4
22. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Sexual Function

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼

23. Are you sexually active?

Yes...Please go to Question 25
No....Please go to Question 29

24. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
25. Have you felt less interest in sex?.....	1	2	3	4
26. **For men only**: Did you have difficulty gaining or maintaining an erection?.....	1	2	3	4
27. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
28. Do you worry about the results of examinations and tests?.	1	2	3	4
29. Do you worry about possible future treatments?.....	1	2	3	4
30. Have you felt uncertain about the future?.....	1	2	3	4

Healthcare Services

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
31. Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?....	1	2	3	4
32. Were you satisfied with the knowledge and experience of your doctors?.....	1	2	3	4
33. Were you satisfied with the speed of implementing medical tests and/or treatments?.....	1	2	3	4
34. Were you satisfied with the frequency of consultations?.....	1	2	3	4

Appendix 9: Preliminary Final LRRC-QoL British version 3

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.

Symptoms **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
4. Have you had any abnormal bleeding or discharge from your rectum?.....	1	2	3	4
5. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
6. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?	1	2	3	4
9. Have you had any weakness of both legs?.....	1	2	3	4
10. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4
11. Have you had pain or discharge from your wound or scars?	1	2	3	4

12. Do you have a urostomy?

Yes...Please go to Question 13
No....Please go to Question 16

13. Did you have problems caring for your urostomy?.....	1	2	3	4
14. Have you felt embarrassed because of your urostomy?.....	1	2	3	4
15. Have you been dependent on others for caring for your urostomy?.....	1	2	3	4

16. Do you have a stoma?

Yes...Please go to Question 17
No....Please go to Question 19

17. Have you felt embarrassed because of your stoma?.....	1	2	3	4
18. Have you had any problems caring for your stoma?.....	1	2	3	4

Psychological Impact

During the past week:

	Not at all	A little	Quite a Bit	Very much
19. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4
20. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Sexual Function

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
21. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
22. Have you felt less interest in sex?.....	1	2	3	4

23. **For men only**: Did you have difficulty gaining or maintaining an erection?.....	1	2	3	4
24. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
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

Healthcare Services

During the past 4 weeks:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
28. Were you satisfied with the information the healthcare professionals gave you about your illness and treatment?...	1	2	3	4
29. Were you satisfied with the knowledge and experience of your doctors?.....	1	2	3	4
30. Were you satisfied with the speed of implementing medical tests and/or treatments?.....	1	2	3	4
31. Were you satisfied with the frequency of consultations?.....	1	2	3	4

Appendix 10: Preliminary LRRC-QoL version 2 - Australia

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.

Symptoms **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
4. Have you had any abnormal bleeding or discharge from your rectum?.....	1	2	3	4
5. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
6. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?	1	2	3	4
9. Have you had any weakness of both legs?.....	1	2	3	4
10. Have you had any difficulty in walking.....	1	2	3	4
11. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4
12. Have you had pain or discharge from your wound(s) or scar(s)?.....	1	2	3	4

13. Do you have a urostomy, nephrostomy or urinary catheter?

Yes...Please go to Question 14
No....Please go to Question 17

14. Did you have problems caring for your urostomy, nephrostomy or urinary catheter?.....	1	2	3	4
15. Have you felt embarrassed because of your urostomy, nephrostomy or urinary catheter?.....	1	2	3	4
16. Have you have been dependent on others for caring for your urostomy?.....	1	2	3	4

17. Do you have a stoma?

Yes...Please go to Question 18
No....Please go to Question 20

18. Have you felt embarrassed because of your stoma?.....	1	2	3	4
19. Have you had any problems caring for your stoma?.....	1	2	3	4

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼

Psychological Impact

During the past week:

20. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4
21. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Sexual Function

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
22. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
23. Have you felt less interest in sex?.....	1	2	3	4
24. **For men only**: Did you have difficulty gaining or maintaining an erection?.....	1	2	3	4
25. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
26. Do you worry about the results of examinations and tests?.	1	2	3	4
27. Do you worry about possible future treatments?.....	1	2	3	4
28. Have you felt uncertain about the future?.....	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?.....	1	2	3	4
30. Were you satisfied with the information the healthcare professionals gave you about your treatment?.....	1	2	3	4
31. Are you satisfied with the diagnosis, treatment and medial follow up provided?.....	1	2	3	4

32. Were you satisfied with the knowledge and experience of your doctors?.....	1	2	3	4
33. Were you satisfied with the speed of implementing medical tests and/or treatments?.....	1	2	3	4
34. Were you satisfied with the frequency of consultations?.....	1	2	3	4

Appendix 11 Preliminary LRRC-QoL version 3 - Australia

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.

Symptoms **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
4. Have you had any abnormal bleeding, discharge or faecal leakage your rectum?.....	1	2	3	4
5. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
6. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?	1	2	3	4
9. Have you had any weakness of either/ or both legs?.....	1	2	3	4
10. Have you had any difficulty in walking.....	1	2	3	4
11. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4
12. Have you had pain or discharge from your wound(s) or scar(s)?.....	1	2	3	4

13. Do you have a urostomy (urine bag), nephrostomy or urinary catheter?

    Yes...Please go to Question 14
    No....Please go to Question 17

14. Did you have problems caring for your urostomy (urine bag), nephrostomy or urinary catheter?.....	1	2	3	4
15. Have you felt embarrassed because of your urostomy (urine bag), nephrostomy or urinary catheter?.....	1	2	3	4
16. Have you have been dependent on others for caring for your urostomy?.....	1	2	3	4

17. Do you have a stoma?

    Yes...Please go to Question 18
    No....Please go to Question 20

18. Have you felt embarrassed because of your stoma?.....	1	2	3	4
19. Have you had any problems caring for your stoma?.....	1	2	3	4

Psychological Impact

During the past week:

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
20. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4
21. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Sexual Function

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
22. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
23. Have you been interested in sex?.....	1	2	3	4
24. **For men only**: How difficult is it for you to gain or maintain an erection?.....	1	2	3	4
25. **For men only:** Have you had ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the past 4 weeks:

	Not at all	A little	Quite a Bit	Very much
26. Do you worry about the results of examinations and tests?.	1	2	3	4
27. Do you worry about possible future treatments?.....	1	2	3	4
28. Have you felt uncertain about the future?.....	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

32. Were you satisfied with the frequency of consultations?..... 1 2 3 4

Appendix 12 Preliminary Final LRRC-QoL - Generic

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.

Symptoms **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
4. Have you had any abnormal bleeding, discharge or faecal leakage your rectum?.....	1	2	3	4
5. **For women only:** Have you had any abnormal discharge or bleeding from your vagina?.....	1	2	3	4
6. **For women only:** Have you had irritation or soreness in your vagina or vulva?.....	1	2	3	4
7. Have you had pain or a burning feeling when passing water/urinating?.....	1	2	3	4
8. Have you had any unintentional release (leakage) of urine?	1	2	3	4
9. Have you had any weakness of either or both legs?.....	1	2	3	4
10. Have you had any difficulty in walking?.....	1	2	3	4
11. Have you had any tingling or numbness in your feet or legs?.....	1	2	3	4

12. Have you had pain or discharge from your wound(s) or scar(s)?.....	1	2	3	4

13. Do you have a urostomy (urine bag)?

Yes...Please go to Question 14
No....Please go to Question 17

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
14. Did you have problems caring for your urostomy (urine bag), nephrostomy, or urinary catheter?.....	1	2	3	4
15. Have you felt embarrassed because of your urostomy (urine bag), nephrostomy or urinary catheter?.....	1	2	3	4
16. Have you have been dependent on others for caring for your urostomy (urine bag)?.....	1	2	3	4

17. Do you have a stoma?

Yes...Please go to Question 18
No....Please go to Question 20

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
18. Have you felt embarrassed because of your stoma?.....	1	2	3	4
19. Have you had any problems caring for your stoma?.....	1	2	3	4

Psychological Impact

During the *PAST WEEK:*

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
20. Have you worried about becoming dependent on others because of your illness?.....	1	2	3	4

21. Have you felt physically less attractive as a result of your disease or treatment?.....	1	2	3	4

Sexual Function

During the *PAST 4 WEEKS:*

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
22. Have you had pain during sexual intercourse or other sexual activity?.....	1	2	3	4
23. Have you been interested in sex?.....	1	2	3	4
24. **For men only**: How difficult is it for you to gain or maintain an erection?.....	1	2	3	4
25. **For men only:** Have you had ejaculation problems (e.g. dry ejaculation)?.....	1	2	3	4

Future Perspective

During the *PAST 4 WEEKS:*

	Not at all ▼	A little ▼	Quite a Bit ▼	Very much ▼
26. Do you worry about the results of examinations and tests?.	1	2	3	4
27. Do you worry about possible future treatments?.....	1	2	3	4
28. Have you felt uncertain about the future?.....	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
32. Were you satisfied with the frequency of consultations?.....	1	2	3	4

Appendix 13: Clinical Information Form for Phase III Data Collection

Patient Identifier: _____

1. Date of Primary Rectal Cancer Operation ____/____/____
2. Neoadjuvant Treatment

   None ☐ Short Course Radiotherapy ☐ Chemoradiation☐Chemotherapy ☐

3. Operation Type

   Local Excision ☐ Anterior Resection ☐ Abdominoperineal Resection ☐

   Hartmann's Procedure ☐ Pelvic Exenteration ☐ Other ☐_____

4. Histology – Primary Cancer

   4.1. TNM Staging _____

   4.2. Dukes Classification _____

   4.3. Margin Status _____

5. Mode of detection of local recurrence

   Symptomatic ☐ Surveillance ☐

6. Date of diagnosis of Local Recurrence ___/___/___
7. Pattern of Local Recurrence

   Anterior ☐ Central ☐ Posterior ☐ Lateral ☐

8. Presence of Concurrent Metastatic Disease

   8.1. Yes ☐ No ☐

   8.2. Number of Sites of Metastatic Disease

   1 ☐ 2 ☐ 3 ☐ 4 ☐

   8.3. Location of Metastatic Disease

Lung ☐ Liver ☐ Cerebral ☐ Bone☐ Other ☐ _____

9. Treatment Intent of Local Recurrence

Curative ☐ Palliative ☐

10. If palliative intent, what is the treatment plan?

Palliative Chemotherapy ☐ Palliative Chemoradiation ☐

Palliative Radiotherapy ☐ Best Supportive Care ☐

11. If curative intent what is the treatment plan?

11.1. Pre-operative treatment

None ☐ Short Course Radiotherapy ☐ Chemoradiation ☐ Chemotherapy ☐

12. Date of operation of LRRC ___/___/___

13. Operation Type _____

14. Margin Status _____

15. Post-operative Treatments

None☐ Short Course Radiotherapy ☐ Chemoradiation ☐ Chemotherapy ☐

16. Current Status

Disease Free ☐ Local re-recurrence ☐ Distant Metastases