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Development of implementation recommendations to facilitate the routine collection of patient-reported outcome measures in prostate and gynaecological cancer patients attending a large NHS Centre

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Development of implementation
recommendations to facilitate the routine
collection of patient-reported outcome measures
in prostate and gynaecological cancer patients
attending a large NHS Centre

Thesis presented in accordance with the requirements for the degree
of Doctor of Philosophy

BY

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March 2023

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Charlotte Louise Moss

2023

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A. Acknowledgements

When I graduated from my Biochemistry degree in 2013, I never could have dreamt that I would be submitting my PhD thesis 10 years later in 2023. It is testament to the unwavering support and mentorship of Professor Mieke Van Hemelrijck that I have been able to complete this thesis – thank you, Mieke, for all the opportunities you have provided me with over the last 7 years.

I must also extend my utmost thanks to my second supervisor, Dr Teresa Guerrero-Urbano. Teresa, your expertise and continued encouragement has been most gratefully received throughout this project.

Special thanks must also be given to Dr Ajay Aggarwal for his guidance and support as Chair of my thesis progression committee. Equally, I am indebted to Dr Kate Haire and Mr Joseph Casey for their wise counsel and the time they invested in this project.

This thesis would not have been possible without the involvement of the patients and healthcare professionals of Guy's Cancer Centre. Above all, I would like to express my enormous gratitude to all the patients who so kindly contributed their time to this project. I would also like to acknowledge Julie Malpass, who assisted me in conducting this research. Julie, this project would not have been possible without your efforts, and I am eternally grateful for your help.

I would also like to give thanks to all my TOUR team colleagues, from both past and present, for their guidance and encouragement. Thank you Anca, Fee, Louis, Katharina, Aida, Maria, Jasmine, Saran, Natalia, Danielle, Rosemary, Lin, Isolt, and Ailbhe. Special thanks must especially be given to Beth, Gincy, Harriet, and Anna who have become friends for life – thank you so much for everything.

Finally, I give the biggest thanks to my family: my Mum and Dad, Lauren, and Paul. Thank you, Mum and Dad, for supporting me through many years of study, for believing in me, and for always being my biggest cheerleaders. To Paul, thank you for being by my side throughout the highs and lows of this PhD, and for supporting me without question. Special mention must also go to our dog, Monty, who has kept me company throughout the write-up process, and my extended Lee family who have provided positivity and laughter throughout. I could not have undertaken this journey without you all.

B. Abstract

Introduction

Patient-reported outcomes (PROs) are an integral component of cancer clinical management providing insight into the health status of patients. PROs are measured using patient-reported outcome measures (PROMs) which are validated self-administered questionnaire tools developed to assess domains of quality of life. Whilst the benefits of using PROMs in the clinical setting are well-established, their routine use is limited as healthcare services face increasing demand, financial deficits, and operational issues. This thesis was therefore undertaken to develop recommendations to facilitate the success of routine clinical PROM collection at a large NHS Cancer Centre. Work was undertaken in the prostate and gynaecological oncology settings, to ensure representation across sexes and within two large tumour groupings.

Methods

This thesis commenced with a systematic review which was undertaken to identify any potential prognostic function of PROMs collected at baseline and follow-up time points. Following this, further systematic reviews were undertaken to identify relevant PROM tools suitable for application in each selected tumour setting. Identified gynaecological PROMs subsequently underwent psychometric assessment according to the CONsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines, to identify the most valid instruments for routine collection. Consensus processes were then undertaken locally with key stakeholders at Guy's Cancer Centre to confirm the selection of PROMs for application in each of the prostate and gynaecological cancer settings.

Furthermore, a feasibility study of routine PROM collection was developed according to the Medical Research Council (MRC) guidance for complex interventions. The feasibility study was conducted in the prostate radiotherapy setting and incorporated comprehensive qualitative and quantitative evaluation to identify key barriers and facilitators impacting the pilot success. A qualitative interview study, developed using the Consolidated Framework for Implementation Research (CFIR), was conducted with 14 healthcare professionals at Guy's Cancer Centre. Additionally, quantitative evaluation of the feasibility study occurred through dissemination of a patient questionnaire which was developed based on Proctor's Implementation Outcomes. Following the identification of barriers, implementation strategies, or recommendations to overcome such contextual factors, were developed guided by the Expert Recommendations for Implementing Change (CFIR-ERIC).

Results

The first systematic review identified a complementary role for the routine collection of PROMs in cancer settings to improve patient quality of life and outcomes. Overall, baseline measurements of global QoL, fatigue, and functioning consistently emerged as independent prognosticators indicative of survival across these tumour types.

Following the employment of the COSMIN criteria, various PROMs were recommended for adoption in the prostate and gynaecologic clinical settings. In the prostate setting, following local consensus, the Expanded Prostate Cancer Index Composite short-form instrument (EPIC-26) was selected for use in the clinical oncology specialty. In the gynaecological cancer setting, the European Organisation for the Research and Treatment of Cancer core module (EORTC QLQ-C30) was selected for collection along with tumour specific supplementary modules.

Twenty consecutive prostate cancer patients were recruited to the feasibility study administering the EPIC-26 at 6 time points following radiotherapy treatment. In total, 14 qualitative interviews with healthcare professionals across tumour sites were completed before thematic analysis was conducted. Key emerging barriers identified as impacting implementation included the availability of staffing resource, information technology integration, and interpretation of PROM scoring for clinical management. Strategies to overcome identified barriers included the development of tailored training programmes for healthcare professionals and patients, as well as clinical and technical championing. Additionally, qualitative data implied the necessity of undertaking local needs assessment to ensure adaptability and scale-up of a routine PROM collection programme.

Additionally, Proctor's Implementation Outcomes were employed to assess the acceptability, feasibility, and uptake of routine clinical PROM collection. This quantitative evaluation of the feasibility study advocated the development of novel teams to support the undertaking of routine clinical PROM collection and ensure compliance. Funding was also identified as a critical component for consideration, to provide the required infrastructure to support routine PROM administration within cancer clinical settings.

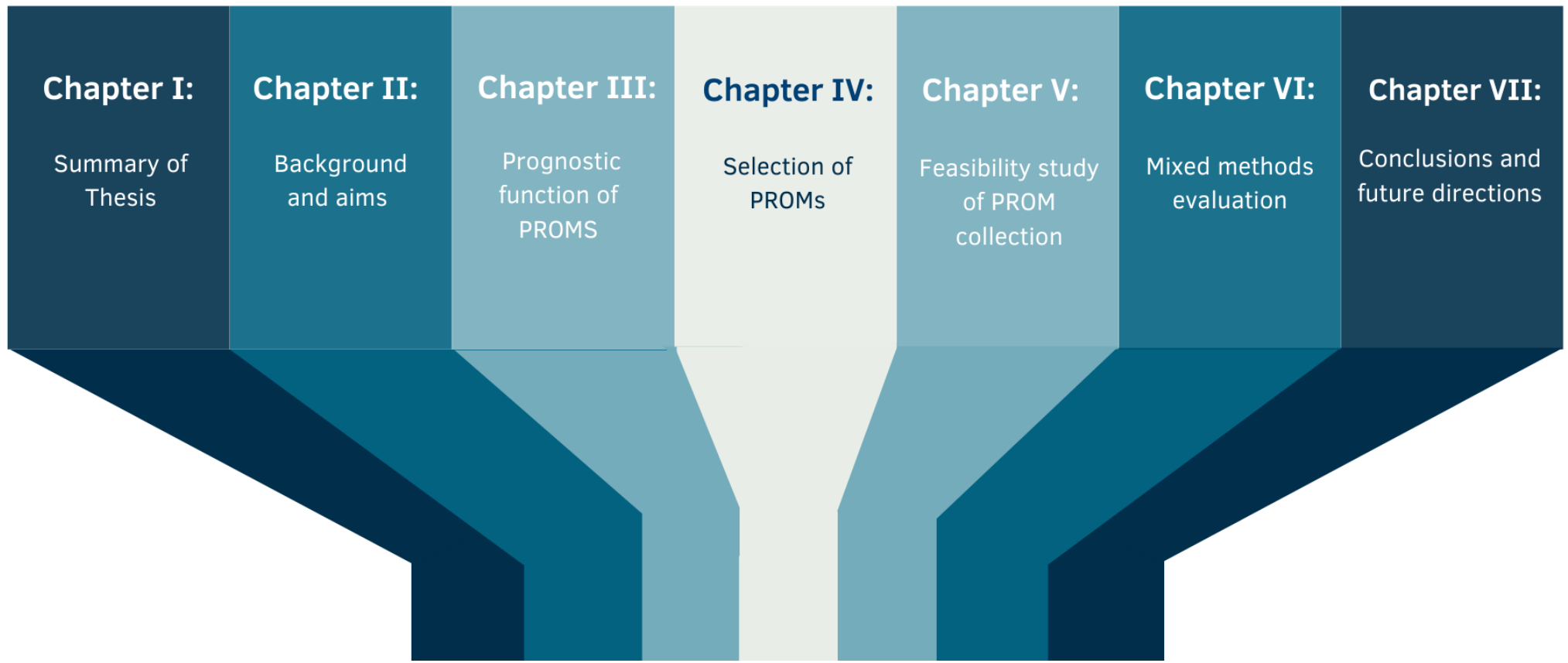
Conclusions

Overall, this thesis presents a clear rationale in support of the implementation of routine clinical PROM collection across cancer settings. Benefits of routine clinical PROM collection were observed for both healthcare professionals and patients, and a novel prognostic role for the collection of PROMs at baseline and follow-up timepoints was identified. The findings of this thesis include the identification of various barriers which affected the success of routine clinical PROM collection at this site. Implementation strategies to address identified barriers have, however, already been

identified, and future studies will be developed to assess each strategies' impact on implementation success.

Overview of Thesis

Development of implementation recommendations to facilitate the routine collection of patient-reported outcome measures in prostate and gynaecological cancer outpatients attending a large NHS Centre.



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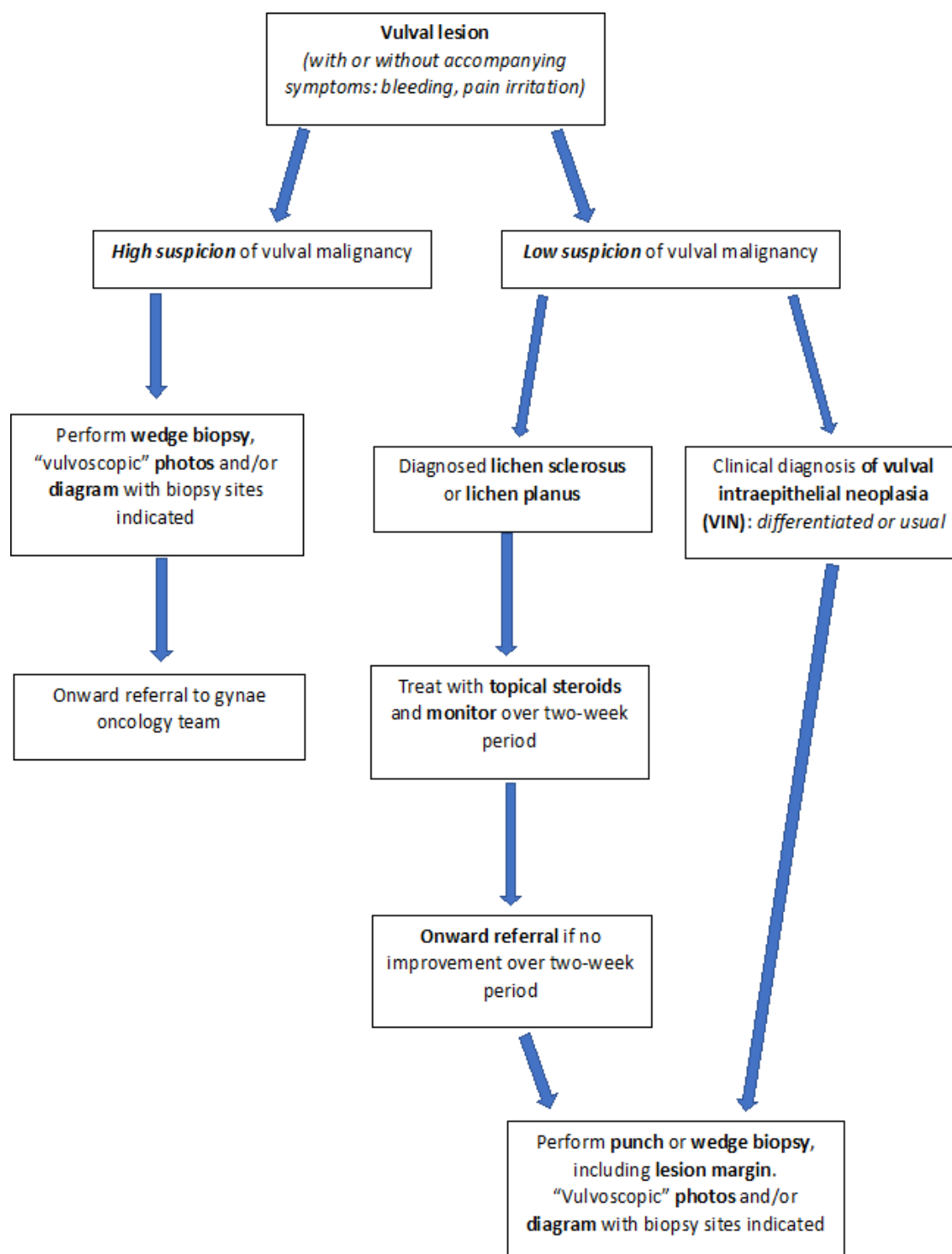
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F. List of Abbreviations

QoL: Quality of life

PROMs: Patient-reported outcome measures

RCTs: Randomised controlled trials

COSMIN: COnsensus based Standards for the selection of health Measurement Instruments

MRC: Medical Research Council

CFIR: Consolidated framework for Implementation Research

CFIR-ERIC: Expert Recommendations for Implementing Change

HRQoL: Health-related quality of life

PCa: Prostate cancer

PSA: Prostate specific antigen

DRE: Digital rectal examination

NICE: National Institute for Health and Care Excellence

mpMRI: Multiparametric MRI

TRUS: Transrectal ultrasound

ISUP: International Society of Urological Pathology
EAU: European Association of Urologists
CPG: Cambridge Prognostic Group
 ProtecT: Prostate Testing for Cancer and Treatment
EBRT: External beam radiation therapy
IMRT: Intensity-modulated radiation therapy
VMAT: Volumetric arc radiation therapy
IGRT: Image-guided radiation therapy
LDR: Low dose rate brachytherapy
HDR: High dose rate brachytherapy
ADT: Androgen deprivation therapy
LHRH: Long-acting luteinising hormone-releasing hormone
PD-1: Programmed cell death protein
PD-L1: Programmed death ligand
ICD: International Classification of Diseases
WHO: World Health Organisation
CA125: Cancer associated antigen – 125
HPV: Human papillomavirus
FDA: US Food and Drug Administration
BGCS: British Gynaecological Cancer Society
HE4: Human epididymis protein 4
HRT: Hormone-replacement therapy
TVS: Transvaginal ultrasound
FIGO: Federation of Gynaecology and Obstetrics
ESGO: European Society of Gynaecological Oncology
ESTRO: European Society for Radiotherapy and Oncology
ESP: European Society of Pathology
EEC: Endometrioid endometrial cancer
LVSI: Lymph-vascular space invasion
LEEP: Loop electrosurgical excision procedure
GOG: Gynaecological Oncology Group

VEGF-A: Vascular endothelial growth factor A

JBI: Joanna Briggs Institute

OS: Overall survival

CROs: Clinician-reported outcomes

PIONEER: IMI PIONEER Consortium

BD40: IMI Big Data for Better Outcomes Programme

HADS: Hospital Anxiety and Depression Scale

EORTC: European Organisation for the Research and Treatment of Cancer

BPI: Brief Pain Inventory

FACT: Functional Assessment of Cancer Therapy

FKSI-15: Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 15 item version

FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms

FSFI: Female Sexual Function Index

MeSH: Medical Subject Headings

AUC: Area under the curve

CFA: Confirmatory factor analysis

CFI: Comparative fit index

DIF: Differential item functioning

ICC: Interclass correlation coefficient

IRT: Item response theory

LoA: Limits of Agreement

MIC: Minimally important change

RMSEA: Root mean square error of approximation

SEM: Standard error of measurement

SDC: Smallest detectable change

SRMR: Standardised root mean residuals

TLI: Tucker-Lewis index

EFA: Exploratory factor analysis

GRADE: Grading of Recommendations Assessment, Development and Evaluation

MOST: Measure of Ovarian Symptoms and Treatment

ICIQ: International Consultation on Incontinence Questionnaire

EPIC: Expanded Prostate Cancer Index Composite

UCLA-PCI: University of California – Los Angeles Prostate Cancer Index

IIEF: International Index of Erectile Function

PCSI: Prostate Cancer Symptom Indices

SPCG-4: Scandinavian Prostate Cancer Group study 4

STAI: State Trait Anxiety Inventory

NPCA: National Prostate Cancer Audit

ROG: Radiotherapy Operating Group

MID: Minimally important differences

SCA: Service Satisfaction Scale for Cancer Care

REDCap: Research Electronic Data CAPture

HIPAA: Health Insurance Portability and Accountability Act

ePROMs: Electronic PROMs

CSV: Comma-separated values

COREQ: Consolidated Criteria for Reporting Qualitative Studies

GSTT: Guy's and St Thomas' NHS Foundation Trust

PRUH: Princess Royal University Hospital

IOF: Proctor's Implementation Outcomes framework

GEM: Grid-Enabled Measures Database

NCI: National Cancer Institute

PPIE: Patient Public Involvement and Engagement

PSFU: Personalised stratified follow-up

Chapter I:

Summary of Thesis

This chapter provides an overview of the structure of the thesis and outlines the research objectives of the PhD.



Chapter I: Summary of Thesis

Chapter II:

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1. Chapter 1: Research objectives and structure of thesis

On a worldwide scale, continued advances in infrastructure and technological innovations are translating into an increase in the numbers of survivors of many types of cancers. These advances are diverse and have resulted from an emphasis on early diagnosis, the development and evolution of cancer therapies, improvements in health infrastructure, and increased availability of healthcare (1, 2). Ageing populations are also contributing, as the risk and incidences of many cancers increases significantly with older age (3). In the UK alone, the Prostate Cancer UK charity estimates that approximately 400,000 men are currently living with and after prostate cancer, and 10-year survival rates for this cancer are estimated to be around 84% (4, 5). For gynaecological cancers, in the UK it is estimated that around 41,000 women are currently living with or after ovarian cancer and 49,000 with or after cervical cancer (6, 7). Cancer research UK estimates that ten-year survival rates for these cancers are 35% for ovarian cancer and 51% for cervical cancer (8, 9). Overall, by 2030, it is projected that over 3 million people will be living with a cancer diagnosis nationally, termed as cancer survivorship (10).

Various definitions of the phrase ‘cancer survivorship’ exist in the literature, but the term was first coined by Mullan et al in 1985 (11). In a published article entitled “Seasons of Survival”, Mullan identified three stages of survivorship including: (1) acute, defined as the diagnosis and treatment of cancer; (2) extended, classified as the period after treatment; and (3) permanent, where survivorship is defined as roughly equivalent to cure. The definition of cancer survivorship has evolved over the proceeding decades, and the National Cancer Institute now employs a comprehensive definition to describe survivorship as: “the health and life of a person with cancer post treatment until end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get healthcare and follow-up treatment, late effects of treatment, second cancers, and quality of life” (12).

As the long-term survival of cancer patients increases, recognition is growing of the need to support each patient during the treatment and survival phase of their illness (13). The 2005 landmark Institute of Medicine report entitled “From Cancer Patients to Cancer Survivor: Lost in Transition” described the medical and psychosocial concerns of cancer survivors and acknowledged a conceptual framework of quality of life covering four domains (physical, psychological, social and spiritual well-being) (14). The conceptualised quality of life model identified four essential components of survivorship care encompassing: (1) prevention of recurrent and new cancers, and of other late effects; (2) surveillance for cancer spread, recurrence, or second cancers and assessment of medical and psychosocial late effects; (3) intervention for the consequences of cancer and its

treatment; and (4) coordination between specialists and primary-care providers to ensure that all of the survivor's health needs are met. However, evidence suggests that at least two-thirds of cancer patients and survivors have physical, psychological, informational, and supportive care needs which are currently unmet within healthcare systems (15). Indeed, a 2008 national population-based survey revealed poorer health and well-being, and higher use of hospital services, among individuals with a cancer diagnosis compared to individuals without a cancer diagnosis (16). The onus therefore lies with healthcare systems to adapt and evolve to support the increasing numbers of cancer patients and survivors, or face further financial burden through increased use of health resources and reduced economic activity. The "Living with and beyond cancer: taking action to improve outcomes" UK governmental report summarised that (1) failure to meet the needs of cancer survivors will prevent outcome improvement, and (2) provision of needs-based support will lead to a cost-effective improvement in survival, quality of life and experience (17).

Quality of life (QoL) is therefore a critical outcome for cancer patients and survivors, and its measurement is considered integral for the provision of clinically meaningful care (18). In this context, patient reported outcome measures (PROMs) provide a clinically relevant, patient-focused, and reliable perspective on quality of life and patient symptom experience. Briefly, PROMs are standardised, validated questionnaires which are completed by patients to indicate perception of their health status or health-related quality of life (19). Empirical evidence supports the use of PROMs in the clinical setting to identify patient concerns, enhance patient-clinician communication and improve patient satisfaction with care in the clinical setting (20, 21). The widespread use of PROMs routinely is, however, limited, with the majority of use occurring within randomised control trials (RCTs) where PROMs are used to monitor health status and quality of life before, during and after experimental treatments. Additionally, PROMs are used in this setting to assess whether the survival benefits of a specific treatment may outweigh any potential side effects, or for choosing between treatment options which offer similar survival benefit (22, 23, 24).

To date, the routine measurement of PROMs in the NHS is mandated in the post-operative setting of hernia repairs, hip and knee replacements, and varicose vein surgical procedures alone. In the NHS specifically, the use of PROMs in routine clinical practice is limited as healthcare services are challenged to sustain high care quality, whilst also facing increased demand and financial austerity (25). Moreover, there is a lack of established standards on what PROMs should be utilised in which setting and how benefits should be measured (26).

This thesis was therefore undertaken to identify components impacting the success of routine collection of PROMs at Guy's Cancer Centre. Guy's Cancer Centre is one of the leading centres in the

UK for cancer treatment and research and is a specialist tertiary referral facility which offers personalised treatment to patients from across the Southeast region. On average, more than 8,000 new cancer cases are diagnosed each year at Guy's Cancer Centre including ~1100 prostate cancer cases and ~450 gynaecological cancer cases. In the context of this thesis, work was undertaken in the prostate and gynaecological cancer settings specifically, to investigate implementation across sexes, and in a large cohort of patients. These two tumour types were selected as use cases, however this thesis aimed to propose implementation recommendations which could ultimately be transferred and applied across all tumour types of Guy's Cancer Centre. Two independent tumour types were selected to facilitate the introduction of routine PROM implementation, in an effective manner.

Overall, this thesis aimed to address a significant gap in the literature related to the translation of PROM implementation into routine clinical settings. Studies were developed to garner critical insight into the key components to be considered when implementing PROMs at Guy's Cancer Centre. Recommendations were developed based on the following studies (reported by chapter):

1. **Chapter III:** A systematic review of the literature was developed to identify **further evidence to support the implementation of routine PROM collection** within cancer clinical settings. The potential prognostic function of collecting PROMs at baseline and follow-up timepoints was investigated, and all tumours of the pelvic-abdominal were included to ensure sufficient appraisable evidence.
2. **Chapter VI:** This project comprised three successive studies which were designed to **address the process of PROM selection** for application in routine clinical cancer settings. Full details of the inclusion criterion, as well as a detailed background section, is included within the chapter.
Firstly, a systematic review of the literature was undertaken to identify relevant PROMs for application.
Secondly, PROMs identified as relevant to gynaecological cancer populations were taken forward and assessed in terms of their validity, reliability, and sensitivity according to the COnsensus based Standards for the selection of health Measurement INstruments (COSMIN) guidelines.
Thirdly, two local consensus processes were undertaken with stakeholders in the prostate and gynaecological oncology settings of Guy's Cancer Centre.
3. **Chapter V:** A **feasibility study of routine clinical PROM collection** was developed in the prostate clinical oncology setting of Guy's Cancer Centre. The feasibility study was developed according to the Medical Research Council (MRC) framework for complex

interventions, and a detailed background of this framework is provided within Chapter V. Background is also provided on the discipline of Implementation Science as well as the Consolidated Framework for Implementation Research (CFIR), which was the framework chosen as the theoretical basis of this feasibility study. High-level patient outcomes from this feasibility study are also reported.

4. Chapter VI: This project comprised quantitative and qualitative evaluation of the feasibility study to identify barriers and facilitators impacting implementation.

A qualitative interview study was conducted with stakeholders involved in the development and undertaking of the feasibility study. Additionally, stakeholders (particularly from gynaecological oncology clinics) who had previous experience or aspirations of using/implementing PROMs were recruited from Guy's Cancer Centre. Both cohorts of participants were recruited to gain insight into the contextual factors impacting routine PROM implementation at this site. The qualitative interview study was designed and analysed using the CFIR. Following the identification of barriers, implementation strategies, or recommendations to overcome such contextual factors, were developed guided by the Expert Recommendations for Implementing Change (CFIR-ERIC) which maps against the constructs of the CFIR.

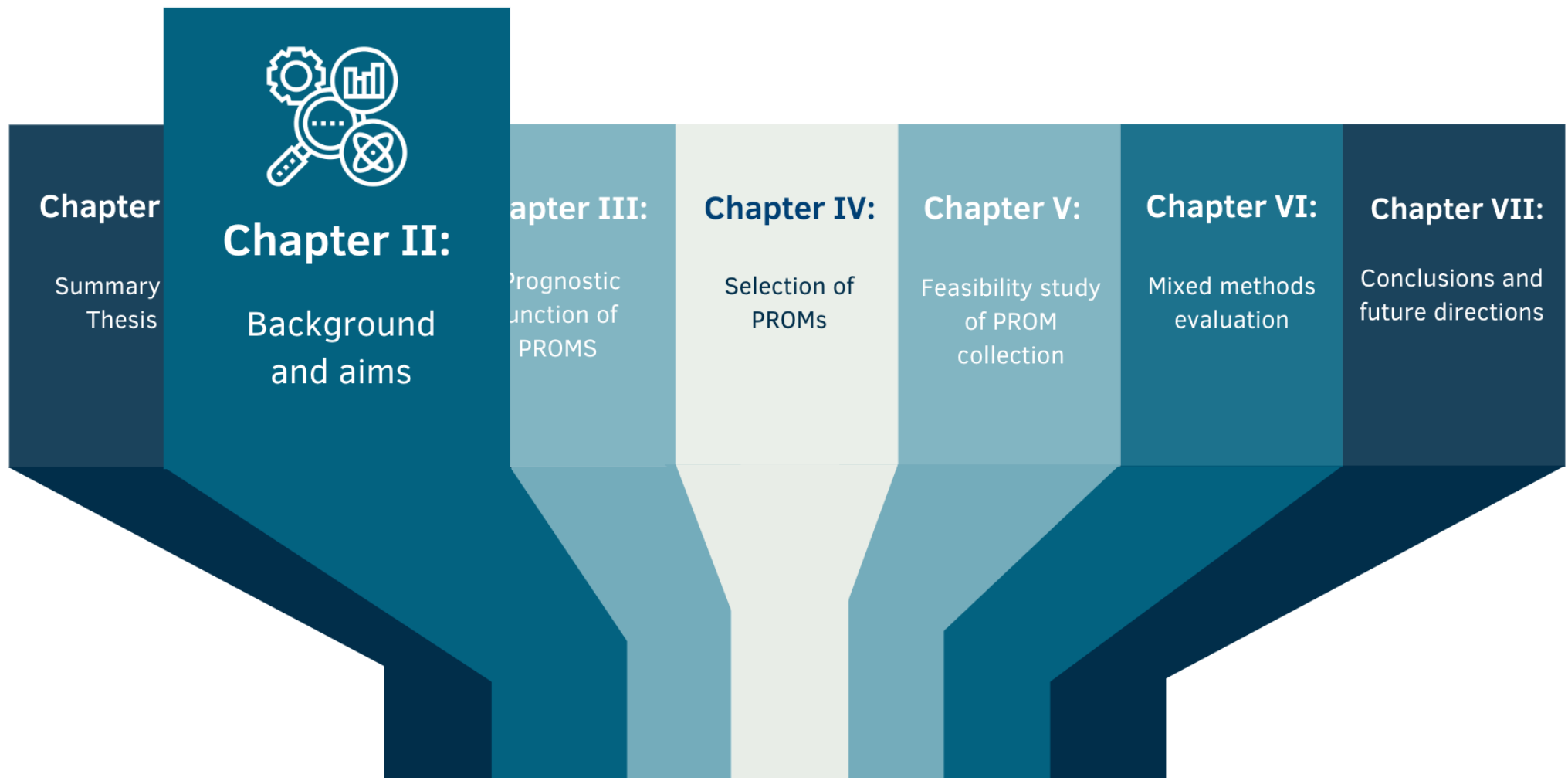
Quantitative evaluation of the feasibility study occurred through dissemination of a patient evaluation questionnaire which was developed based on Proctor's Implementation Outcomes. Patient and stakeholder compliance with the feasibility study was evaluated at the provider-level.

The next chapter (Chapter II) provides a detailed background on the epidemiology, biology, and management of prostate and gynaecological cancers. A comprehensive background on health-related quality of life in the context of cancer is also provided. Chapters III-VI describe the methods and results of the studies outlined above, in chronological order. As detailed above, a comprehensive background of Implementation Science, the Consolidated Framework for Implementation Research (CFIR), and the MRC framework for complex interventions is included in Chapter V. Brief background on Proctor's Implementation Outcomes is also provided within the rationale section of Chapter VI (section 6.2) to provide context to the reader. Finally, Chapter VII provides an overall conclusion as well as suggestions for the future directions of this research.

Chapter II:

Background and aims

A comprehensive background is provided for quality of life, and prostate and gynaecological cancers. Definitions are included as well as a detailed background on disease epidemiology, biology, and management.



2. Chapter 2: Background

2.1 Quality of Life and Cancer

In the field of oncology, the combination of advances in existing therapies, the continued emergence of novel therapeutics, and a focus on early detection methods is translating into improved rates of survival for cancer patients. Concurrently, patient quality of life has emerged as a fundamental objective of cancer care, to facilitate understanding of the impact of disease at an individual patient level (18). High quality clinical care now requires cancer patients to provide information to their clinical teams related to how they are feeling, their disease symptoms, and any side effects of treatments. This concept of health-related quality of life (HRQoL) is a multidimensional and integral construct which focuses on the impact of treatment and disease management, and multiple definitions have been proposed. The following section of this thesis will outline the history of health-related quality of life, the various definitions of the construct, and methods for measuring.

2.1.1 History of Health-Related Quality of Life

The concept of quality of life as an important component of healthcare emerged in the early 1970s. The origins of the concept, interestingly, did not emerge in the healthcare setting specifically, but rather as part of a wider political agenda at the time concerned with more generalised societal issues. During the social crisis of the 1960s and 1970s where, despite economic improvements, an increase in societal issues such as crime was witnessed, quality of life emerged as a potential method to assess social progress (27, 28).

In parallel with societal changes, the 1960s and 1970s saw an explosion in the development of novel medical devices including new forms of cancer therapy (29). In particular, at the end of World War II, a plethora of new chemotherapy-based treatment agents were approved. Despite the obvious gains observed from these new treatments in terms of survival, medicine also began to recognise the apparent disadvantages of this evolution including loss of ability to ensure patient quality of life (30). Dempster et al noted that patients' often 'paid a heavy price in terms of physical discomfort, significant risk of irreversible or fatal physiological changes, and long periods of hospitalisation' (31). The notion of quality of life hence emerged as a method to assess the costs to patients of these technological advances.

At the same time, a parallel exploration was occurring in terms of debating the ethics of extending the quantity of life at the expense of quality of life. In 1976, Brody et al provided a summary of the issues of medical ethics and included quality of life as a key factor along with informed consent,

shared decision-making, and communication (32). From this point onwards, quality of life was recognised as a common currency of medical evaluation and outcome.

Moreover, during the second part of the 20th century, the number of patients diagnosed with chronic diseases increased exponentially as a result of new technologies and an ageing population. In these cohorts, use of survival was deemed a poor indicator of medical success. Quality of life measurement could therefore replace mortality as a key outcome in these populations to accurately reflect success (33).

As of the end of the 20th century, HRQoL has become integrated as a standard means of evaluation in healthcare. Since its emergence in the 1970s, the number of publications in the field of quality of life has increased exponentially.

2.1.2 Definition of Health-Related Quality of Life

Prior to widespread use of the term ‘health-related quality of life’, the terms ‘quality of life’ and ‘health status’ were frequently penned. The term ‘health-related quality of life’ was first introduced in literature referring to health status measures; for example, Kaplan et al penned the term in discussions on ‘quality-adjusted life years’ (34). Following the initial introduction, the term was adopted in various influential publications and its usage increased in the 1970s.

The definition of HRQoL is contentious and at least four separate definitions exist in the literature (35). One such definition of the term refers to “how well a person functions in their life, and his or her perceived well-being in physical, mental, and social domains of health” (36). In this context, functioning refers to an individual’s ability to carry out predefined activities, whilst well-being concerns an individual’s subjective feelings. A further definition of HRQoL links the term directly to QoL describing that “quality of life is an all-inclusive concept incorporating all factors that impact upon an individual’s life. Health-related quality of life includes only those factors that are part of an individual’s health” (37). The third utilised definition of HRQoL focuses on the elements of QoL which are impacted by health. In this setting, HRQoL is defined as “those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment” (38). Finally, the fourth established definition of HRQoL centres on the value of health, whereby values or utilities are employed to calculate quality-adjusted life years and assess the benefits of health technologies (39).

When defining HRQoL, distinguishing between QoL and health status is problematic due to the overlap of different definitions in each space. Overall, HRQoL can be defined as a subjective and multidimensional concept which incorporates domains related to physical, mental, emotional, and social functioning. For the purposes of this thesis, the third definition of HRQoL will be employed to

describe aspects of self-perceived well-being which are related to, or affected by, the presence of disease or treatment. This definition was selected as this thesis concerns the routine implementation of patient-reported outcome measures (PROMs) to evaluate self-perceived well-being specifically in the context of cancer and its treatment.

2.1.3 Measuring Health-Related Quality of Life

In recent decades, the importance of measuring HRQoL has become widely accepted across medical communities as a critical component of cancer management. One published study, by Tanaka et al observed that clinicians and medical students perceived HRQoL to be as important a component as overall survival in the treatment decision making process (40). Furthermore, a study by Morris et al undertook a survey of 260 senior oncologists to investigate the perception of HRQoL in the clinical setting (41). The results of this study presented that 80% of study participants believed that HRQoL should be collected routinely from cancer patients.

Despite the obvious benefits of measuring HRQoL, the subjective nature of the construct translates into challenges with accurate measurement. Various components of HRQoL, such as pain, cannot be directly observed, and clinicians often underreport or misinterpret both functioning and symptoms. One study by Stephens et al used the Rotterdam Symptom Checklist to assess how > 700 lung cancer patients and their clinicians reported functioning and symptoms related to HRQoL (42). The study observed that the clinicians consistently under-assessed the level of functioning and symptoms compared to the patient themselves, and concluded that the worse the patient's symptoms, the less likely the clinician was to report them as severe. As such, HRQoL is usually assessed using patient-reported questionnaires, or patient-reported outcome measures.

2.1.3.1 Patient-reported outcome measures

Patient reported outcome measures, or PROMs, are standardised, validated questionnaires which are completed by patients to indicate their perception of their own HRQoL (19). PROMs are self-report instruments which can be utilised across the treatment landscape to better understand the efficacy and efficiency of specific treatments, and provide insight into patients' perceptions of their general health or health in relation to a specific disease (43). The outcomes-based definition of PROMs distinguishes these questionnaires from alternate instruments used to measure patient experience across the care process (44).

Two distinct categories of PROMs exist: those designed to measure patient's perceptions of their general health ("generic") or those developed to indicate perceptions of health in relation to specific diseases or conditions ("disease-specific") (45). The purpose of generic health status instruments is to measure the well-being of an individual based on certain dimensions, which generally relate to

measures of physical and social functioning, pain, or anxiety and depression (46). In contrast, disease-specific measures include questions which are sensitive to small changes in health-status that are related to a given disease, disability, or surgery (46). Such instruments have the ability to detect subtle changes in health or functional status.

The next sections (2.2 and 2.3) of this Chapter provide a detailed background related to the disease epidemiology, diagnosis, treatment, and adverse effects of prostate and gynaecological cancers, which were the two tumour types selected as use cases in this thesis.

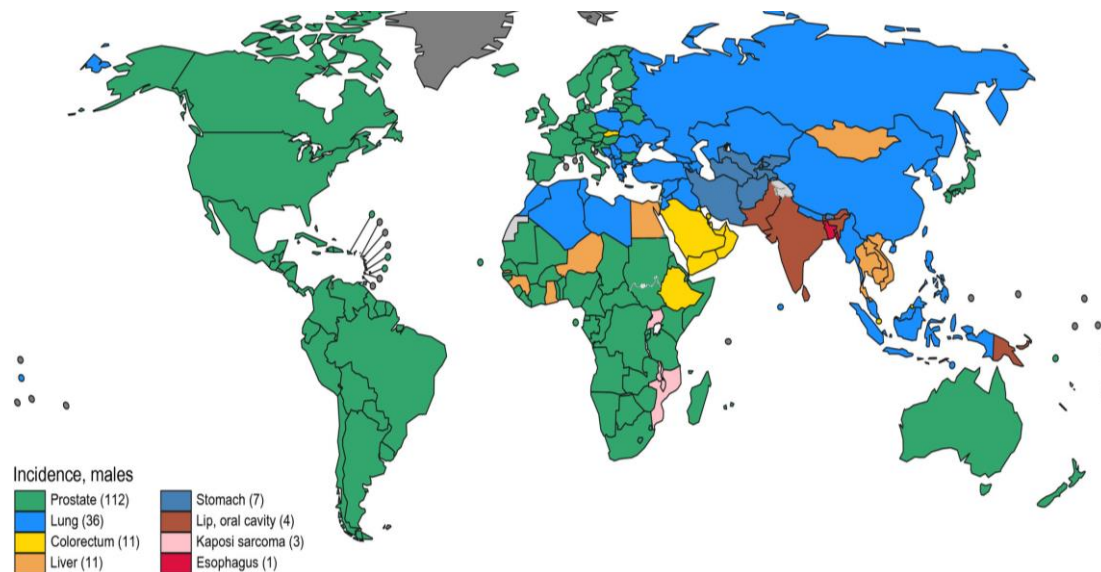
2.2 Background of Prostate Cancer

The prostate is a walnut-sized gland located between the bladder and urethra which functions to produce the prostatic fluid of semen (47). Prostate cancer (PCa) is a disease which occurs when cells within the prostate gland begin to divide uncontrollably forming cancerous cells (4). The anatomical positioning of the prostate sometimes results in symptomatic disease, with common symptoms of PCa including increased frequency of urination, frequent nocturnal urination, and increased urgency in urination (48). The large majority of diagnosed PCa cases are classified histologically as acinar adenocarcinomas which are tumours which first develop in the outer gland cells. Other, rarer, subtypes of PCa include neuroendocrine tumours, transitional cell carcinomas and squamous cell carcinomas, however these collectively account <10% of PCa diagnoses overall (49).

2.2.1 Epidemiology of prostate cancer

PCa is the most common cancer in men in the UK (Figure 1) and, in 2020, the disease accounted for approximately 13,168 deaths (50). In 2020, the UK had an all-age age-standardised rate (ASR) of incidence of 80 per 100,000 which was higher than the ASR for Europe overall (63 per 100,000). The cumulative lifetime risk of PCa for men in the UK was calculated as 20% (compared to 16% cumulative lifetime risk in Europe) and the all-age ASR for mortality was 12.4/100,000 (51). In the Western world, the use of PSA testing as a method of early detection is leading to an increase in the identification of indolent PCa cases, which in turn is translating into overall increased incidence rates (52). Age-standardised mortality rates have, however, decreased in Europe which may be attributed to evolving treatment regimens and superior care systems (53).

1. Figure 1: Most common cancer per country. The figure legend includes the number of countries represented per tumour type (excludes non-melanoma skin cancer). Figure source: GLOBOCAN 2020 and graph production: IARC. Property of the World Health Organisation.



2.2.2 Diagnosis of prostate cancer

2.2.2.1 Prostate cancer screening

In the UK, there is currently no approved screening programme for PCa, however a number of diagnostic tests can be employed clinically as an initial method for detecting disease. The first, and most commonly utilised method, is via a blood sample which measures prostate specific antigen (PSA). Prostate specific antigen is a protein produced by both normal and malignant cells of the prostate gland. The PSA test was initially approved for use by the FDA in 1986 to monitor disease progression in men previously diagnosed with PCa but, since the late 1990s, has become more widely used as a diagnostic test, resulting in an increase in the numbers of men diagnosed with PCa (54). Generally, a PSA level of ≥ 3.0 -4.0 ng/mL is considered an elevated result which is potentially indicative for the presence of PCa, however it is important to consider that a raised result can also be attributed to either inflammation or enlargement of the prostate not related to carcinoma (55). PSA testing is often used in conjunction with a digital rectal examination (DRE) to detect abnormalities in the size and structure of the prostate (56). Oftentimes, a PCa can be palpated on examination due to their common occurrence in the peripheral zone of the prostate (57).

Following initial clinical triage using PSA and DRE, the National Institute for Health and Care Excellence (NICE) guidelines now stipulate the use of multiparametric MRI (mpMRI) as a first line of investigation for men suspected of having PCa (58). These national guidelines were amended following the conclusion of the PROMIS and PRECISION clinical trials which both presented evidence

to recommend the use of imaging to risk stratify men prior to biopsy, thereby preventing unnecessary and invasive investigative tests in low-risk patients (59, 60). The guidelines, updated in 2019, now specify offering mpMRI-influenced prostate biopsy for men with a Likert score ≥ 3 . Five-point Likert scales can be used to standardise the reporting of MRI's and predict the existence of clinically significant prostate cancer (61).

2.2.2.2 Pathological diagnosis of prostate cancer

An investigative biopsy of the prostate tissue is typically offered to men with elevated PSA, palpable mass on DRE, and/or a Likert score of ≥ 3 as calculated using mpMRI (62). A biopsy is a procedure in which small samples of the prostate (cores) are removed to be examined histologically, usually using a core needle biopsy technique in PCa specifically. The biopsy is often guided using a combination of imaging methods including transrectal ultrasound (TRUS) and mpMRI. Historically, biopsies were mostly undertaken transrectally, however, more recently, transperineal biopsies, which result in fewer side effects, have been widely adopted (63). When cancer is identified in the biopsy cores, different histological characteristics of the disease are graded according to the Gleason system.

The Gleason scoring system is applied to assess the prognosis of men diagnosed with PCa based on their biopsy samples (64). More aggressive cancers, with a worse prognosis, are assigned a higher Gleason score. The Gleason scoring system was originally developed following the observation that cancerous cells can be categorised into one of five distinct patterns ranging from normal prostate tissue to high grade, highly mutated cells. Pathologically, one Gleason score is assigned to the most predominant pattern observed within the biopsy cores, and a second score is given to the second most observed pattern (65). These two scores are then added together to provide an overall Gleason score (example, 3+4) with overall pathological scores ranging from 2-10. If only one pattern is present, the score is doubled to yield this overall Gleason score. Additionally, the biopsy samples are graded according to International Society of Urological Pathology (ISUP) classifications which categorise the samples into five grade groups (66). These grade groups incorporate the Gleason scoring and are utilised to predict PCa outcomes (67). The Gleason scoring groups and corresponding ISUP grades, last modified in 2014, are presented in Table 1.

Table 1: International Society of Urological Pathology (ISUP) grading system with corresponding Gleason scores

Gleason Score	ISUP Grade
≤ 6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4, or 3 + 5, or 5 + 3)	4
9 to 10	5

Following a histological diagnosis of prostate cancer, both the European Association of Urologists (EAU) and NICE guidelines recommend assignment of a risk stratification category derived from information on PSA, Gleason Score, and clinical staging (elucidated from MRI imaging) (68). The EAU risk group classification is based on the 3-tiered D'Amico risk stratification tool which was developed initially to assess 5-year risk of treatment failure based on clinical factors. The tool works to classify patients with prostate cancer into low, intermediate, or high-risk groups, and is presented in Table 2. In contrast, the five-tiered Cambridge Prognostic Group (CPG) classification was adopted in 2021 by NICE to replace the 3-tiered D'Amico risk stratification tool (69). Both classifications assist in informing clinical decision making for the management of PCa.

Table 2: Risk groups as classified by the European Association of Urologists for the biochemical recurrence of localised and locally advanced prostate cancer.

Low risk	Intermediate risk	High-risk	
PSA < 10ng/mL and Gleason score < 7 (ISUP grade 1) and cT1-cT2a	PSA 10-20ng/mL or Gleason score 7 (ISUP grade 2 or 3) or cT2b	PSA > 20ng/mL or Gleason score > 7 (ISUP grade 4 or 5) or cT2c	Any PSA Any Gleason Score (any ISUP score) cT3-cT4 or cN+
Localised			Locally Advanced

N.B. Risk groups based on D'Amico model of risk stratification, ISUP; International Society of Urological Pathology, PSA; prostate-specific antigen

2.2.3 Management of prostate cancer

There are various treatment options available for men with PCa including active surveillance, watchful waiting, prostatectomy, radiation therapy, and hormonal therapies (70).

2.2.3.1 Deferred Treatment

Active surveillance and watchful waiting are collectively classified as deferred treatments (71). Active surveillance is offered to patients with low-risk PCa for whom immediate treatment is not required (72). In these low-risk cases, patients are monitored at regular intervals to determine the most appropriate timepoint for curative treatment to be offered. These patients remain under close

observation consisting of regular repeat PSA testing, clinical examination, MRI imaging, and biopsies (73). Utilising large cohorts with long-term follow-up, the viability of active surveillance as an adequate treatment option for men with low-risk PCa has been investigated. A study of 1818 men on active surveillance identified 93% 10-year overall survival and 99.9% 10-year cancer-specific survival. This large study included 60-month median follow-up and was published by Tosoian et al in 2015 (74). Additionally, published evidence from the Prostate Testing for Cancer and Treatment (ProtecT) trial observed no significant difference in the overall mortality of men on active monitoring compared with men undergoing radical prostatectomy or radical radiotherapy. This evidence is limited, however, by the trial employing active monitoring rather than traditional active surveillance (75). Active monitoring is accepted as a significantly less stringent monitoring strategy in terms of clinical follow-up, imaging and repeat biopsies.

Guidance regarding the selection process for active surveillance remains limited owing to a paucity of published randomised control trials. A panel of experts from the EAU therefore recently undertook a combined systematic review and consensus process to identify the available protocols for active surveillance and provide recommendations on the threshold criteria for offering this treatment option. This work, published as the DETECTIVE study, supported previously published criterion of: ISUP grade 1 disease, clinical stage T1c or cT2a, PSA < 10ng/mL for consideration of active surveillance (76, 77).

Watchful waiting is indicated for men with limited life expectancy who therefore are deemed unsuitable for curative treatment (78). These patients are often significantly co-morbid and are clinically monitored for any evidence of local or systemic progression (79). Once progression is identified, this cohort are offered palliative treatment for symptom management only.

2.2.3.2 Radical Prostatectomy

A radical prostatectomy is a surgical procedure which is performed to remove the prostate, with capsule intact, and the surrounding seminal vesicles (80). The procedure is offered in the curative setting and aims to fully eliminate the cancer whilst preserving the function of other organs located in the pelvic cavity. Since the 1980s, when radical prostatectomy was first popularised, surgical approaches have evolved to now include laparoscopic and robotic techniques (81). The oncological outcomes of radical prostatectomy have been investigated in multiple multi-centre RCTs including the SPCG-4 trial which was conducted using low and intermediate risk patients in the pre-PSA era. This study concluded a cancer-specific survival at 23 years of 80.4% (82). The more recent ProtecT trial of PCa patients of a similar risk category identified 10-year cancer-specific survival of 99% (75).

2.2.3.3 Radiation Therapy

External beam radiation therapy (EBRT) is a technique which utilises high-energy rays, delivered from outside the body, to destroy or slow the growth of cancer cells (83). Currently, the gold standard approach for EBRT includes intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) with image-guided RT (IGRT) (84). Intensity-modulated and volumetric arc radiation therapies function by continuous and dynamic adaptation to the contours of the target lesion. VMAT boasts shorter treatment times compared to IMRT, typically shortening treatment time by a two-to-three-minute period (85).

For men with localised PCa undergoing radical beam radiotherapy, hypofractionated radiotherapy (60 Gy in 20 fractions) using image-guided intensity modulated radiation therapy can be offered unless contraindicated (62). Hypofractionated radiotherapy differs from conventional external beam radiotherapy as it offers the delivery of fewer, larger doses of radiotherapy (86). According to published NICE guidelines, conventional radiotherapy (74Gy in 37 fractions) should be offered to those patients for whom these higher intensity doses are not suitable (62).

Brachytherapy is an alternate radiation therapy treatment option which is usually administered during the early stages of PCa (87). There are two approved types of brachytherapy: low-dose rate (LDR) and high-dose rate (HDR). LDR brachytherapy uses radioactive seeds which are permanently implanted into the prostate whereas HDR employs a radioactive source which is only temporarily introduced to the prostate (88, 89). In LDR, the radiation dose is delivered over a period of weeks and months whilst in HDR, the full dose is delivered within minutes.

2.2.3.4 Systemic Therapy

Androgen deprivation therapy (ADT) functions by suppressing the production of the male androgen hormones (testosterone and dihydrotestosterone) which in turn slows the growth of prostate cancer cells (90). Androgens are male sex hormones which are essential for the growth and functioning of the prostate, reproductive and sexual functioning, and the development of sexual characteristics during puberty. Androgens also promote the growth of prostate cancer, through binding and activation of androgen receptors on prostate cells. Androgen deprivation can be achieved through several methods, each of which ultimately involve suppression of the secretion of testicular androgens.

Previously, castration, or surgical removal of the testes, was considered the traditional method of ADT. Surgical castration is achieved via a procedure called bilateral orchiectomy (91). Long-acting luteinising hormone-releasing hormone (LHRH) agonists are currently the principal form of ADT employed in clinical practice (91). Chronic exposure to synthetic analogues of LHRH agonists result in

the downregulation of LHRH-receptors which, in turn, suppresses secretion of luteinising hormone and follicle-stimulating hormone, and therefore inhibits the production of testosterone (92).

Castration is usually achieved within a 2–4-week period. To date, no survival differences between the use of orchiectomy and LHRH agonists has been reported in the literature (93).

Luteinising hormone-releasing hormone antagonists function mechanistically by inhibiting pituitary gland production of follicle-stimulating hormone and luteinising hormone (94). The antagonists bind immediately to the LHRH receptors, leading to a rapid decrease in production of each hormone and testosterone.

Castration-resistant prostate cancers are a class of disease which cease to respond to the use of ADT (95). The biological mechanisms which underpin this loss of sensitivity to ADT are unknown, but eventually men with prostate cancer will show evidence of disease progression despite castration. For men with metastatic castrate-resistant prostate cancer, first line treatments include abiraterone, enzalutamide and docetaxel (96). Abiraterone and enzalutamide are both classified as anti-androgens (97).

Anti-androgens are oral compounds which are classified as either steroidal or non-steroidal. Both classes of these compounds compete directly with androgens at the receptor level leading to either unchanged or slightly elevated levels of testosterone (98).

Docetaxel is a cytotoxic chemotherapy agent which mechanistically inhibits cell division and tumour proliferation, ultimately leading to cell apoptosis (99). Docetaxel is a standard first-line chemotherapy used in metastatic prostate cancer which is often administered in combination with ADT (96).

More recently, novel forms of systemic treatments for prostate cancer have been developed and introduced into routine practice. One such example is the development of immune checkpoint inhibitors, which have been introduced into the metastatic castration-resistant prostate cancer setting in recent years. The role of immune checkpoint inhibitors is to regulate the immune system and prevent an immune response against healthy cells of the body. Checkpoint proteins exist on the surface of cells to ensure immune equilibrium, and immune checkpoint inhibitors function by preventing binding of these proteins with their partner proteins. Such inhibition prevents inactivation of immune cells and primes the immune response to kill tumour cells (100). In the PCa setting, currently approved immune checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death ligand (PD-L1) (101).

2.2.3.5 Treatment by risk group

The main risk for patients diagnosed with low risk PCa is over treatment and therefore any patient diagnosed with this stratification of disease should first be offered active surveillance (102). For patients with low-risk disease and a projected life expectancy > 10 years, radical prostatectomy and/or radical radiation therapy can be considered as alternatives to active surveillance should this option not be suitable (75).

Radical prostatectomy can be offered to patients with intermediate risk PCa (103). In this risk category, the risk of positive lymph nodes ranges from 3.7-20.1%, and it is recommended that an extended lymph node dissection also be undertaken where the estimated risk of lymph node involvement exceed 5% (104, 105). Combination short term ADT (over a period of 4-6 months) and IMRT/VMAT radiation therapy is also recommended for the intermediate risk PCa patients (106). LDR brachytherapy can be offered to PCa patients classified as intermediate risk and where evidence exists of good urinary function prior to treatment (107). Fractionated HDR brachytherapy may additionally be considered, however there exists a paucity of data to support its use in this risk group.

Patients with high-risk localised prostate cancer are at an increased risk of disease progression. The prostate cancer specific mortality rates for this risk group are 28.8% at 10 years and 35.5% at 15 years respectively (108). In cases where the tumour is not fixed to the pelvic wall and where there is no invasion of urethral sphincter present, radical prostatectomy is a reasonable treatment option. Multimodal treatment in the form of radiotherapy or ADT can be administered in the adjuvant setting. In this risk group, the combined multimodal treatment strategy should consist of IMRT/VMAT with longer term ADT which is administered over a 2 to 3-year period (109). Furthermore, a combination brachytherapy boost in the form of HDR brachytherapy with supplementary external beam radiation therapy, can be considered (110).

There exists a paucity of evidence to direct recommendations for the optimal treatment of locally advanced PCa (111). In the absence of published research, a local treatment in combination with a systemic treatment is indicated as the best course of action provided the patient is sufficiently fit. Radical prostatectomy in combination with external beam radiation therapy and/or ADT is established as a suitable treatment option for this patient cohort. In addition, it is widely accepted that prescription of long-term ADT combined with radiation therapy is a viable treatment option with good reported overall survival rates (112, 113, 114).

Approximately 5-10% of prostate cancers exhibit synchronous pelvic nodal involvement at diagnosis (96). For this cohort specifically, there exists an overlap in local and systemic treatment options.

Indeed, the management of such disease (cN1M0) is usually based on long term prescription of ADT in combination with a local treatment (115). Such addition of a combination local treatment has been assessed in various trials which collectively suggest a survival advantage for patients receiving either radiation therapy or radical prostatectomy with ADT compared to ADT alone. However, one further published study which investigated addition of a brachytherapy boost concluded that there was no association with overall survival when this boost was delivered to ADT plus EBRT PCa patients (116).

The AFU-GETUG 12 trial compared the impact of administration of docetaxel in addition to ADT. The results of this study, along with a separate meta-analysis of docetaxel trials, concluded a survival advantage for those patients' receiving docetaxel with ADT (117). Additionally, the STAMPEDE trial of 1974 men with *de novo* locally advanced PCa randomised patients to receive ADT alone or ADT plus abiraterone, with or without enzalutamide (97). In the trial, radiotherapy was mandated for patients with N0 disease and recommended for those with N1 disease. The STAMPEDE trial concluded that those patients receiving combination therapy had significantly improved metastasis-free and overall survival compared to those receiving ADT alone ($HR = 0.53$, 95% CI: 0.39-0.71), ($HR=0.54$, CI: 0.39-0.76) respectively.

2.2.4 Adverse effects of PCa therapies

2.2.4.1 Surgery

A lack of consensus on the reporting of surgical complications, coupled with the introduction of different surgical techniques, has resulted in wide variation in the reporting and incidence of post radical prostatectomy complications. Erectile dysfunction is currently accepted as the most common complication of radical prostatectomy, with dry ejaculation, changes in the quality of orgasm function, and pain on orgasm also reported (118, 119). The second most commonly reported complication is urinary incontinence, but changes to urinary flow and issues related to voiding of the bladder are also frequently noted (120).

2.2.4.2 Radiotherapy

The ProtecT trial investigated toxicity for PCa patients treated with EBRT and 6 months of ADT, and bowel toxicity was the most reported treatment side effect (121). Such bowel toxicities included persistent diarrhoea, increased urgency of bowel movements and/or incontinence, and rectal bleeding.

For brachytherapy treatment, a proportion of patients report significant urinary complications following implantation of the radioactive therapy (122). These aforementioned urinary complications include, but are not limited to, urinary retention and incontinence.

2.2.4.3 Hormonal Therapy

According to published literature, the use of ADT impacts multiple psychological factors pertaining to sexual function, mood, cognitive function, and depression (123). One published RCT assessed quality of life in PCa patients with non-localised disease and described that those treated with ADT noted a significant decline in spatial reasoning, abilities, and memory at 1-year follow-up (124). This patient cohort also experienced increased depression, anxiety, fatigue, and irritability during treatment. A further trial reported increased worry, physical discomfort, and poorer overall health for PCa patients receiving LHRH agonists as compared to bilateral orchiectomy (125).

In terms of sexual function, up to 93% of PCa patients on ADT report cessation of sexual activity (126). Androgen deprivation therapy is associated with both reduced libido and reduced ability to gain and maintain erections.

Hot flushes, or the sudden feeling of intense warmth in the upper body, is another commonly described side effect of ADT (126).

Equally, ADT use is associated with an increased risk of bone fracture as a consequence of increased bone turnover and decreased bone mineral density (127). In fact, severe fractures in men are associated with an increased risk of death, and PCa patients should therefore be offered bone mineral density evaluation through DEXA prior to commencement of ADT (128).

Androgen deprivation therapy is linked to a number of metabolic effects including alterations to lipid levels, insulin resistance, and prevalence of metabolic-like syndrome. Metabolic syndrome is defined as a cluster of independent conditions which occur concurrently and increase the risk of cardiovascular disease (129). Indeed, cardiovascular disease is a common cause of death in these PCa patients and ADT prescription is therefore often accompanied by counselling on preventative measures such as weight loss, increased exercise, and smoking cessation (130).

Fatigue is a further common side effect of ADT, and regular exercise is recommended as the gold standard mitigative measure (131).

2.3 Background of gynaecological cancers

Gynaecological cancers arise in the female reproductive tract; a body system which is composed of the ovaries, Fallopian tubes, uterus, cervix, and vagina. Cancers can develop in any of the female reproductive organs and occur as a result of abnormal proliferation of cells. As such, the overarching gynaecological cancer group comprises five female specific malignant neoplasms: cervical, ovarian and endometrial, and the less common vaginal and vulval cancers (132). The *International Classification of Diseases* (ICD) is a globally recognised diagnostic tool which was developed initially

as a healthcare classification system for use in epidemiological, health management and clinical settings (133). The system is maintained by the World Health Organisation (WHO) and seeks to map health conditions into corresponding generic categories through assignment of a designated code. The 10th iteration of the ICD classification was first published in 1994 and malignant neoplasms of the female genital organs are categorised using C51 to C58 codes (134). Details of the ICD-10 codes and morphological classifications of each of the female genital malignant neoplasms are included in Table 3.

Table 3: ICD-10 codes and morphological subtype classifications for each of the female genital malignant neoplasms

ICD-10 Code	Organ	Morphological subtype classifications
C51	Vulva	Squamous cell carcinoma Extramammary Paget's disease Malignant melanoma
C52	Vagina	Squamous cell carcinoma Adenocarcinoma (botryoid) Rhabdomyosarcoma
C53	Cervix uteri	Squamous cell carcinoma Neuroendocrine carcinoma Adenocarcinoma
C54	Corpus uteri	Endometrial adenocarcinoma Malignant mixed Müllerian tumours Leiomyosarcoma
C55	Uterus (unspecified)	
C56	Ovary	Surface epithelial tumours Serous adenocarcinoma Endometrioid adenocarcinoma Mucinous adenocarcinoma Clear cell carcinoma Germ cell tumours Dysgerminoma Yolk sac tumour Choriocarcinoma Mature and immature teratoma Sex cord-stromal tumours Granulosa cell tumour Sertoli-Leydig cell tumour
C57	Other unspecified female genital organs	
C58	Placenta	Hydatidiform mole Placental site trophoblastic tumour Choriocarcinoma

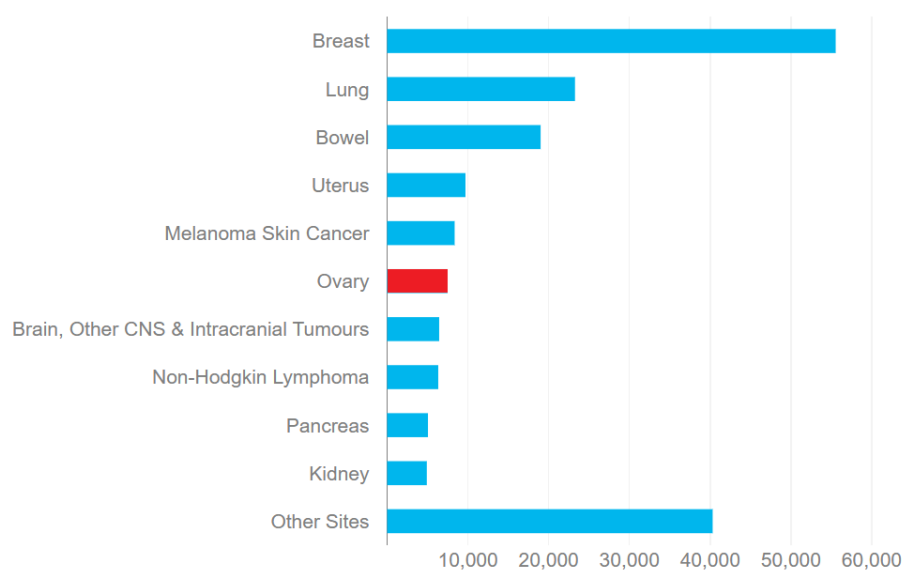
Although symptoms of gynaecological cancers differ by each of the five specific tumour types, abnormal vaginal bleeding or discharge is common (with the exception of vulval cancers). Additional common symptoms include pelvic pain or pressure, urinary frequency and urgency (with or without the presence of constipation), and itching, burning, or vulval pain (135).

2.3.1 Epidemiology of gynaecological cancers

2.3.1.1 Ovarian Cancer

As of 2020, ovarian cancer was the 7th most common cancer in women worldwide accounting for ~314,000 new diagnoses (50). In total, 4.7% of all cancer related deaths in women were attributed to ovarian cancer in this year. In the UK specifically, between 2016-2018, there were 7,495 new reported cases of ovarian cancer and it is currently the 6th most common cancer in females (8). Incidence rates for ovarian cancer in the UK are highest in females aged between 75-79 years and it is the second most diagnosed gynaecological malignancy after endometrial cancer. Despite incidence rates of ovarian cancer remaining stable over the last decade in the UK, by 2035 incidence is projected to increase by 15% to 32 cases per 100,000 females.

2. Figure 2: Graph adapted from Cancer Research UK to illustrate the 10 most common female cancers in the UK and the comparative number of new diagnoses of ovarian cancer annually.



2.3.1.2 Endometrial Cancer

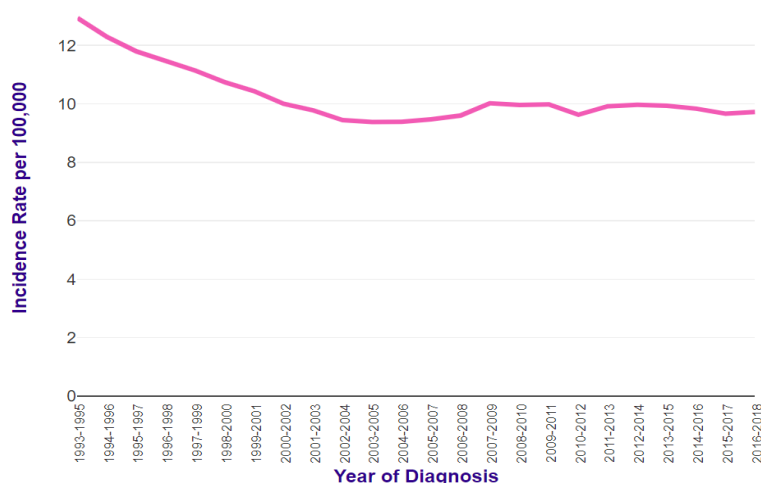
According to global statistics, in 2020, endometrial cancer accounted for ~417,000 new cases (2.2% of all new cancer diagnoses) and ~93,000 deaths (50). In the UK, between 2016 and 2018, ~9,700 new endometrial cancer cases were reported, and the malignancy is purported as the 4th most common cancer in females (136). Like ovarian cancer, incidence rates of endometrial cancer in the UK are highest in females aged between 75-79 years with 27% of all new diagnoses occurring in this

age category. Incidence rates of endometrial cancers have increased by approximately 59% since the early 1990s but are projected to fall by 7% to 35 cases per 100,000 females by 2035. Mortality rates have also increased by around 25% over the last decade and are projected to rise further to 9 deaths per 100,000 females by 2035.

2.3.1.3 Cervical Cancer

Cervical cancer is the most commonly diagnosed gynaecological malignancy worldwide accounting for an estimated 604,000 new cases in 2020 alone (50). Around 90% of all cervical cancer diagnoses occur in low- and middle-income countries, and the cancer is one of the leading causes of cancer death in females reflecting 7.7% of all cancer related deaths worldwide in 2020. Compared to worldwide incidence rates, the UK and other Western countries boast a far lower number of new diagnoses annually (9). Indeed, since the early 1990s, cervical cancer incidence rates have decreased by a quarter in the UK and the malignancy now accounts for less than 1% of all cancer deaths in females (around 850 deaths annually). The age-standardised incidence rates for cervical cancer in females in the UK are presented in Figure 3 and reflect the time period of 1993-2008. Such decrease in both the incidence and mortality rates for cervical cancers in higher-income countries can be attributed to the introduction of successful screening programmes and society-based preventative control measures such as the human papillomavirus (HPV) vaccination programme.

3. Figure 3: Age-standardised incidence rates of cervical cancer in UK females between 1993-2008. Adapted from Cancer Research UK: Cervical cancer incidence statistics | Cancer Research UK



2.3.1.4 Vaginal cancer

According to worldwide incidence rates published in 2020, vaginal cancers are the rarest malignancy comprising 0.1% of all new cancer cases and cancer-related deaths (50). In the UK, around 250 new diagnoses of vaginal cancer are reported annually and incidence rates for the disease have remained

stable since the early 1990s (137). An estimated 104 deaths occur from vaginal cancer annually in the UK with approximately half of these deaths arising in females aged 75 years or above. Over the last 50 years, vaginal cancer mortality rates have decreased by 49% and now account for less than 1% of any cancer death both in females alone, and in males and females combined.

2.3.1.5 Vulval cancer

Globally, vulva cancer is classified as a rare malignancy with approximately 45,000 new cases diagnosed in 2020 (50). In the UK, an estimated 1,400 new diagnoses of vulval cancer occur annually accounting for less than 1% of all new cancer cases in females (138). The malignancy also accounts for < 1% of all cancer deaths in the UK with around 470 deaths reported annually. Mortality rates for vulval cancer have remained stable over the past decade in the UK and 7/10 of the deaths reported annually occur in females aged 75 years or older.

2.3.2 Diagnosis of gynaecological cancers

2.3.2.1 Gynaecological cancer screening methods

2.3.2.1.1 Ovarian cancer screening

Despite widespread research spanning several previous decades, there currently exists no national screening programme for ovarian cancer in the UK. The tumour marker cancer-associated antigen (CA)125 was first described by Bast in 1981 and, to date, remains the most widely investigated biomarker for ovarian cancer (139). Previous research identified that approximately 85% of women with epithelial ovarian cancer had elevated CA125 > 35 U/mol, and these elevated levels were present in approximately 50% of early-stage diagnoses and 90% of advanced stage disease cases (140). The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial recruited 200,000 women between 2001-2005 to investigate the applicability of a screening programme for ovarian cancer utilising the CA125 marker (141). This randomised control trial, which combined serum CA125 interpretation with transvaginal ultrasound and clinical assessment, identified that it was possible to detect ovarian cancer with high levels of sensitivity and specificity. Despite the success of detection, however, no significant differences in death were observed for the multimodal screening group at either the 11.1 years or 16.3 years follow-up timepoints. The results of this trial therefore concluded that an ovarian cancer screening programme could not be recommended in the general population.

2.3.2.1.2 Cervical cancer screening

Screening programmes have been widely implemented in the Western world for the detection of cervical cancers. The majority of cervical cancer cases are caused by the human papillomavirus (HPV), and currently there exists four vaccinations which have been prequalified by the World

Health Organisation (WHO) to be administered to girls between the ages of 9 and 14 years old prior to commencement of sexual activity (142). The four approved vaccinations protect against development of HPV strains 16 and 18 which are known to cause more than 70% of cervical cancers (143). Specifically, the 9-valent vaccine protects against development of 5 additional oncogenic HPV types which are attributed to a further 20% of cervical cancer cases (144).

In the UK, regular screening for cervical cancer is offered through the NHS to all women between the ages of 25 and 64 years (145). In the Western world, cervical cancer screening typically occurs using the Papanicolaou smear and cytology-based methods (146). Published in 1943, the collaborative research of Dr George Papanicolaou and Dr Herbert Traut derived that both normal and abnormal smears of the vagina and cervix could be correctly classified microscopically (147). This procedure, named a Pap smear, is low cost, easily reproducible, and became the gold standard for cervical cancer screening in the UK from the early 1960s onwards (148). Three decades later, in the 1990s, advances in cytotechnology, or the study of cells at an individual level, led to the development of liquid-based cytology products (149). In contrast with the conventional Pap smear methodology, where a fixative was applied to the cervical sample on a slide, the liquid-based test involves sampling and cell transfer to a liquid medium before automated processing. The majority of cervical cancer screening tests now use this method, despite various studies identifying no discernible differences in the sensitivity and specificity of the detection of cervical intraepithelial neoplasia (the precursor to cervical cancer) compared to conventional Pap smears (150).

Since the early 2000s, cervical cancer screening guidelines stipulate the addition of HPV testing with cervical cytology (151). The first US Food and Drug Administration (FDA) approved test for high-risk HPV was introduced in 2003 and identifies the presence of virus by either signal or nucleic acid amplification techniques. To date, four additional tests have been approved, and all are now used in combination with cytology for cervical cancer screening. In recent years, trials have also commenced to investigate the use of HPV testing alone as the primary modality for screening. Such trials established both superior and equivalent rates of effectiveness of cervical cancer screening as compared with cytology alone, and it is predicted that this method may therefore eventually become the gold standard screening modality (152, 153).

2.3.2.1.3 Endometrial, vaginal and vulval screening

Currently, there exists no approved screening methodology for endometrial, vaginal or vulval cancers. In the case of endometrial malignancies, many women present with abnormal bleeding in the early stages of disease and hence screening in the general population is not indicated (154). Vaginal and vulval are the rarest of the gynaecological cancers, and the literature around these

tumours is sparse. As such, the value of screening in these cancers is yet to have been explored (155).

2.3.2.2 Diagnostic methods for gynaecological cancers

2.3.2.2.1 Diagnosis of ovarian cancers

According to the most recent ovarian cancer guidelines published by the British Gynaecological Cancer Society (BGCS), sequential testing with CA-125 and ultrasound is recommended for women presenting to primary care with symptoms suggestive of disease (156). Urgent referral is subsequently indicated if test results are abnormal or in cases where women have presented with a palpable abdominal mass (156).

Following referral to secondary care providers, the BGCS endorses further tumour marker diagnostic tests to facilitate diagnosis (157). In cases where CA-125 levels are elevated, further CA-125/CEA ratio and CA19-9 panel tests are recommended prior to primary debulking surgery. Assessment of clinical levels of human epididymis protein 4 (HE4) is also advocated for younger women because, unlike CA-125, this biomarker is not raised in cases of pelvic inflammatory disease or endometriosis (158).

Radiological staging is performed in women with presumed ovarian cancer to provide further clinical diagnostic information related to the extent of disease and any potential metastases. CT imaging of the thorax, abdomen and pelvis is recommended as best practice to define the extent of disease and to exclude the presence of distant macroscopic disease spread (159).

In cases where advanced ovarian cancer is suspected, a confirmed histological tissue diagnosis is mandated. Histological tissue diagnosis is usually undertaken using image-guided biopsy techniques (157).

2.3.2.2.2 Diagnosis of endometrial cancers

The 2021 BGCS endometrial cancer guidelines stipulate offering of abdominal, speculum and pelvic examination to women presenting with postmenopausal bleeding (160). Such examinations are also indicated clinically for women experiencing unscheduled bleeding on hormone-replacement therapy (HRT), persistent intermenstrual or irregular bleeding, or haematuria. As per published NICE guidelines, premenopausal women experiencing persistent intermenstrual or persistent irregular bleeding should be offered histological assessment via urgent gynaecology assessment pathways (161). Such histological assessment should also be offered to women with infrequent heavy bleeding who are obese or have polycystic ovary syndrome, or to women taking tamoxifen.

As per best practice guidelines, women experiencing postmenopausal bleeding whilst not using HRT should be referred via 2-week wait pathways to a rapid access gynaecology clinic (162). Women with unscheduled bleeding who do use HRT should first cease use of the therapy for a period of 6 weeks prior to any subsequent referral to a rapid access clinic. According to the BGCS, similar referrals should also be completed for women utilising tamoxifen with concurrent postmenopausal bleeding or persistent intermenstrual bleeding with negative pelvic examination (162).

Transvaginal ultrasound (TVS) with double thickness endometrium measurement is indicated by the BGCS as the gold standard initial investigation for any women presenting with postmenopausal bleeding (162). Double thickness measurement of the endometrium refers to the maximum anterior to posterior thickness as measured at the intersection between the uterine walls. In the UK, transvaginal ultrasound followed by endometrial biopsy is accepted as the most cost-effective method for diagnosis, owing to the low prevalence of endometrial cancers (<15%). The BGCS employ a clinical cut-off of $\geq 4\text{mm}$ when measuring endometrial thickness using transvaginal ultrasound (162). Supporting published literature proposes that the risk of cancer is approximately 7.3% for postmenopausal women with vaginal bleeding with a defined thick endometrium ($> 5\text{mm}$). Further literature investigating cut-off levels of 3mm, 4mm, and 5mm for endometrial thickness identified sensitivities of 98%, 95% and 90% respectively for excluding endometrial cancer (163). When utilising an endometrial thickness cut-off of 4mm, a high negative predictive value of >99% was observed for transvaginal ultrasound, therefore reliably excluding the necessity of endometrial biopsy for women with endometrial thickness $< 4\text{mm}$ (164).

In asymptomatic postmenopausal women using HRT it is clinically accepted that measurement of endometrial thickness alone is not useful diagnostically but a cut-off thickness limit of 8mm can be employed where necessary. In symptomatic postmenopausal women using HRT or tamoxifen, endometrial biopsy is indicated if endometrial thickness exceeds 5mm (165).

A definitive diagnosis of endometrial cancer can only be confirmed by histological sampling. The BGCS guidelines specify endometrial biopsy for women with postmenopausal bleeding with an endometrial thickness of $> 4\text{mm}$ (162). Endometrial sampling can occur using either Pipelle® or Vabra© aspirator devices, both of which have been independently verified as accurate in detecting endometrial cancer (166). Contrarily, published NICE guidelines advise endometrial biopsy only in the context of hysteroscopy for pre- and peri-menopausal women (161). A hysteroscopy permits visualisation of the uterine cavity through insertion of a telescope instrument and is beneficial for detecting structural irregularities.

In line with published BGCS guidelines, hysteroscopy should also be considered in scenarios where clinical concern is on-going despite negative endometrial biopsy (162). Equally, hysteroscopy should be considered in cases where endometrial biopsy is not feasible, or for women with irregularities observed on ultrasound or at high risk of endometrial cancer.

2.3.2.2.3 Diagnosis of cervical cancers

Oftentimes, early-stage cervical cancer is asymptomatic and is detected incidentally through an abnormal result on screening smear test (160). Classic symptoms of cervical cancer are also attributable to a number of benign conditions and women can remain asymptomatic until the disease has reached a late stage. Symptoms associated with cervical cancer include abnormal vaginal bleeding, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding (167). Further symptoms include dyspareunia, abnormal vaginal discharge, haematuria, and changes in bladder and bowel functioning. Bone pain due to metastatic disease, and weight loss, can occur in advanced disease.

If cervical cancer is suspected following routine screening, women are referred for colposcopy which is a medical diagnostic procedure that allows visual examination of the cervix, vagina and vulva (168). A colposcope functions as a lighted binocular, and acetic acid solution is applied to the surface of the cervix to improve visualisation of any potentially abnormal areas (169). Areas of the cervix which turn white after the application of acetic acid, or which have an abnormal vascular pattern, are considered for biopsy (170). Three key types of biopsy can be employed; (1) punch biopsy whereby a circular blade is used to remove a tissue sample, (2) cone biopsy which uses a laser or scalpel to remove a large cone-shaped piece of tissue from the cervix, or (3) endocervical curettage using a curette to collect samples from the lining of the endocervical canal (171). In line with BGCS guidelines, punch biopsy methods are preferable and multiple punch biopsies are indicated to increase reliability (168).

2.3.2.2.4 Diagnosis of vaginal cancers

Symptoms associated with vaginal cancer include appearance of a palpable lesion in the vaginal opening, postmenopausal or intermenstrual bleeding, abnormal discharge, or pain during sexual intercourse (172). Occasionally, early-stage vaginal cancer can be detected during routine cervical cancer screening resulting in urgent referral to a specialised gynaecology department (173). In the NHS, women with palpable lesions in the vaginal canal or opening to the vagina are referred for urgent investigation via local 2-week wait pathways.

Primary investigations for women presenting with suspected vaginal cancer include pelvic examination and colposcopy (173). Excision or punch biopsy is usually undertaken to detect vaginal

cancer cells or vaginal intraepithelial neoplasia, which is the precursor of vaginal malignancy (174). Further diagnostic imaging including MRI, CT and PET-CT may also be employed to diagnose and stage vaginal cancers.

2.3.2.2.5 Diagnosis of vulval cancers

There currently is no screening provision for the detection of vulval cancers. It is, however, well established that a number of background conditions increase the risk of disease. The most common histological subtype of vulval cancer is squamous cell carcinoma which occurs both independently and dependently of human papillomavirus (175). HPV-independent vulval squamous cell carcinoma develops from a background of vulval dermatoses, namely lichen sclerosus and lichen planus, and differentiated vulval intraepithelial neoplasia (176).

Lichen sclerosus is a disease of the skin which is characterised by the appearance of white patches in the anogenital regions (177). Such white patches are thinner than normal skin layers and cause symptomatic itching, pain, bruising, tearing, and bleeding in the anogenital areas. In contrast, lichen planus is defined as a chronic inflammatory condition which can affect the skin, nails, hair, and mucous membranes, and causes itchy, flat bumps which appear purple in colour (178). Various studies have independently investigated the association between lichen sclerosus and risk of subsequent vulval cancer and estimate an increased risk of between 2.6-6.6% (179).

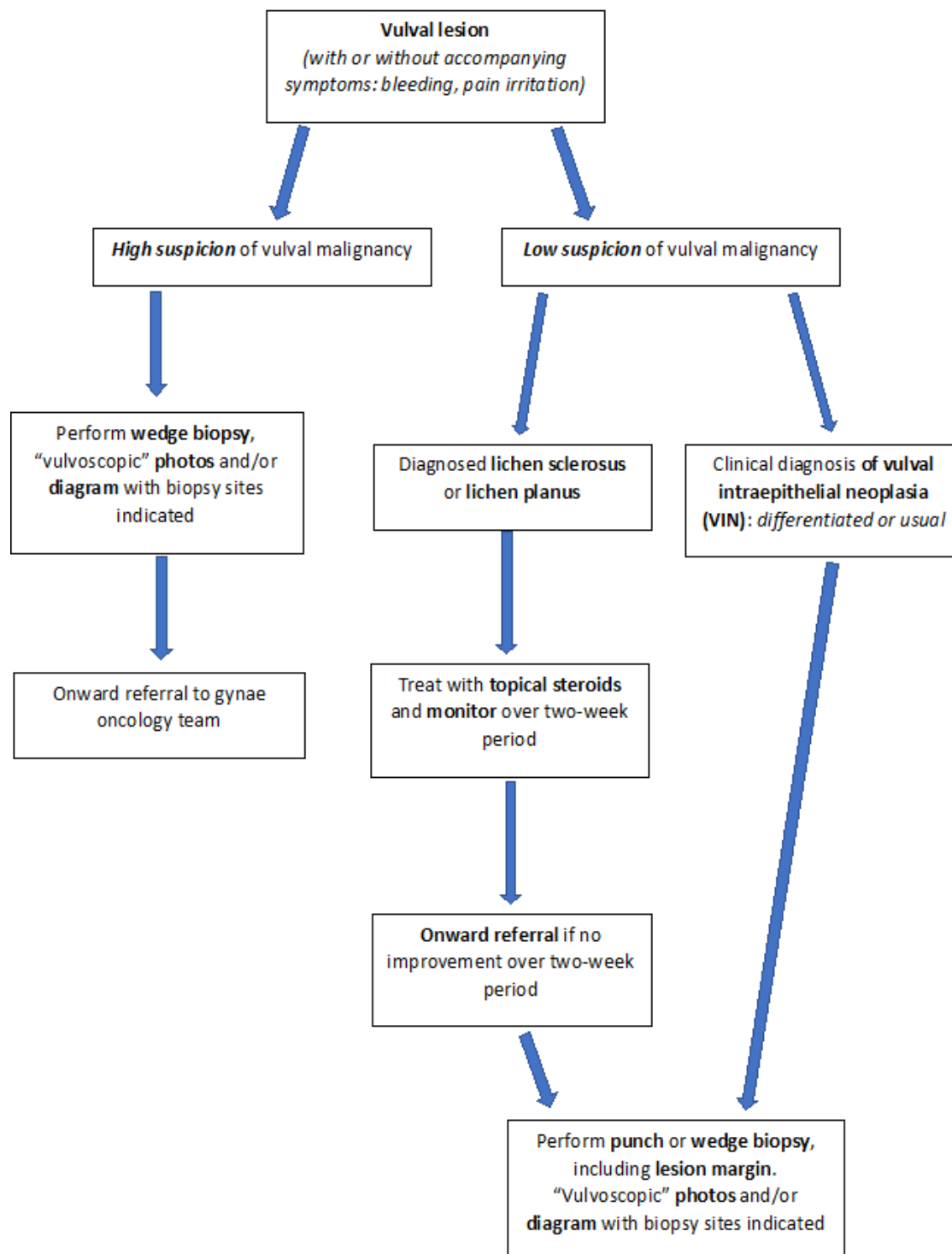
The majority of HPV-related vulval squamous cell carcinomas are caused by HPV 16, and usual type vulval intraepithelial neoplasia represents the pre-malignant lesion for these tumours (180). The recent development of prophylactic vaccinations against various strains of HPV is translating into significant decreases in the prevalence of preinvasive vulval lesions, and it is predicted that the relative proportions of HPV-associated vulval cancers will continue to decrease as vaccine coverage increases (181).

A preponderant number of vulval cancers present clinically with a specific, visible lesion (182). The BGCS specify immediate referral to a specialised cancer centre for women who present with clinical features highly suspicious of vulval cancer, i.e., presence of a fungating tumour with or without palpable lymph nodes (183). Note, fungating tumours are defined by the existence of ulcerating tumours which appear on the surface of the skin. In such cases, diagnostic punch biopsies may not adequately sample the tumour.

Published guidelines favour the use of incisional biopsies (typically punch or wedge biopsy) for diagnosis and specify sampling of adequate depth for differentiation between superficially invasive lesions and invasion > 1mm (183). As best practice, “vulvoscopy” images with scale indication

should be obtained pre and post biopsy to inform clinical decision making. At a minimum, a detailed diagram of the vulva including details of each biopsy site should be generated. A flowchart outlining the investigative process for suspicious vulval lesions is outlined in Figure 4.

4. Figure 4: Flowchart outlining Investigative pathways for the diagnosis of vulval cancer. Adapted from British Gynaecological Cancer Society guidelines.



2.3.2.3 FIGO Staging of Gynaecologic Tumours

The original Federation of Gynaecology and Obstetrics (FIGO) staging system was developed in 1928 following a commissioned call undertaken by the Radiological Sub-Committee of the Health Organisation and overarching League of Nations (184). This work centred around the production of uniform statistical information on radiotherapeutic treatment methods for uterine cervical cancer and, in turn, led to the development of an international classification system to allow grouping of such patients based on clinical examination and anatomic extent of disease. These classifications were adopted on a more worldwide scale following the publication of various 'Annual Reports' produced by the Health Organisation from 1934 onwards, and in 1958 FIGO became the official patron of this work.

In recent years, the FIGO staging systems for all gynaecological malignancies have shifted from a basis of clinical information alone to incorporate surgical-pathological characteristics of disease (184). Primarily, each staging system was developed to guide treatment decision-making. The most up-to-date staging systems for each of the five gynaecological tumour types is presented in Table 4.

Table 4: The updated Federation of Gynaecology and Obstetrics staging system for each gynaecological malignancy.

	2014 FIGO ovarian staging system	2018 FIGO cervical staging system	2009 FIGO endometrial staging system	2009 FIGO vaginal staging system	2021 FIGO vulval staging system
Stage 1					
<i>IA</i>	Tumour limited to one ovary (capsule intact); no tumour on ovarian surface; no malignant cells in the ascites or peritoneal washings	Invasive carcinoma diagnosed only by microscopy, with maximum depth of invasion <5mm	Tumour confined to corpus uteri with no or <50% myometrial invasion	Tumour confined to vagina and < 2cm in size	Tumour confined to vulva, tumour size ≤ 2cm and stromal invasion ≤ 1mm
<i>IB</i>	Tumour limited to both ovaries (capsule intact); no tumour on ovarian surface; no malignant cells in the ascites or peritoneal washings	Invasive carcinoma with measured deepest invasion ≥ 5mm (> than Stage IA), lesion limited to cervix uteri	Tumour confined to corpus uteri with invasion >50% of the myometrium	Tumour confined to vagina and > 2cm in size	Tumour confined to vulva, tumour size > 2cm or stromal invasion > 1mm
<i>IC</i>	Tumour limited to one or both ovaries with: surgical spill or capsule rupture or malignant cells in ascites or peritoneal washings				
Stage 2			Tumour invades the cervical stroma but does not extend beyond the uterus		Tumour of any size with extension to lower one-third of the urethra, vagina, anus and negative lymph nodes
<i>IIA</i>	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	Involvement limited to the upper two-thirds of the vagina without parametrial involvement		Tumour extends through vaginal wall but without involvement of the pelvic wall and is < 2cm	

<i>II B</i>	Extension to other pelvic intraperitoneal tissues	With parametrial involvement but not up to the pelvic wall		Tumour extends through vaginal wall but without involvement of the pelvic wall and is > 2cm	
Stage 3					
<i>IIIA1</i>	Positive retroperitoneal lymph nodes only: Metastasis up to or > 10mm in greatest dimension	Carcinoma involves the lower third of the vagina with no extension to the pelvic wall	Tumour invades the serosa and/or adnexae	Tumour of any size with or without pelvic wall invasion and/or nephrosis, inguinal lymph node spread	Tumour of any size with disease extension to upper 2/3rds of the urethra, vagina, rectal mucosa, or regional lymph node metastases ≤ 5mm
<i>IIIA2</i>	Microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph nodes			Tumour invasion of pelvic wall and/or nephrosis, without lymph node involvement	
<i>IIIB</i>	Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	Extension to the pelvic wall and/or causes hydronephrosis or non-functioning kidney	Vaginal and/or parametrial involvement		Regional lymph node metastases > 5mm

<i>IIIC</i>	Macroscopic peritoneal metastasis beyond the pelvis up to 2cm with or without metastasis to retroperitoneal lymph nodes (including extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent	Metastases to the pelvic and/or para-aortic lymph nodes		Regional lymph node metastases with extracapsular spread
Stage 4					
<i>IVA</i>	Pleural effusion with positive cytology	Spread to adjacent pelvic organs	Tumour invasion of bladder and/or bowel mucosa	Tumour invasion of the bladder or rectum	Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases
<i>IVB</i>	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity)	Spread to distant organs	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes	Spread to distant organs	Spread to distant organs

With the exception of endometrial cancer, gynaecological cancers are managed according to FIGO staging (185). For endometrial cancers, in 2014, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly undertook a consensus process to develop risk-stratification guidelines for tailored endometrial cancer management (186). These guidelines stratify endometrial cancer patients to provide estimations on the risk of metastases at diagnosis and future risk of recurrence, and incorporate the endometrial FIGO staging system. The ESGO-ESTRO-ESP guidelines were updated in 2021 to incorporate molecular risk classification and are included below in Table 5 with accompanying FIGO staging information (187).

Table 5: ESGO-ESTRO-ESP published guidelines outlining prognostic risk stratified groups for endometrial cancer patients.

Risk Group	Tumour Characteristics
Low	Stage IA, Endometrioid endometrial cancer (EEC) grade ½, No lymphovascular space invasion (LVSI)
Intermediate	Stage IB, EEC grade ½ without LVSI or Stage IA, EEC grade 3 without LVSI or Stage IA non-endometrioid endometrial cancer (NEEC)
High-intermediate	Stage I EEC, with substantial LVSI regardless of grade/depth of invasion or Stage IB EEC grade 3 regardless of LVSI status or Stage II
High	Stage III-IVA with no residual disease or Stage I-IVA NEEC with myometrial invasion and no residual disease
Advanced metastatic	Stage III-IVA with residual disease or Stage IVB

2.3.3 Management of gynaecological cancers

There are various treatment options available for women diagnosed with gynaecological cancers including a number of site-specific surgical procedures, radiotherapy, brachytherapy, systemic treatments and hormonal therapies.

2.3.3.1 Surgery

2.3.3.1.1 Hysterectomy

A hysterectomy is a surgical procedure which is undertaken to remove the uterus (188). There are several definitions of hysterectomy, including total hysterectomy where the cervix is removed with the uterus. Total hysterectomy is the most commonly undertaken procedure clinically. A total hysterectomy can further include removal of the adnexae (ovaries and fallopian tube) and this procedure is named a total hysterectomy with bilateral salpingo-oophorectomy. A supra-cervical

hysterectomy refers to the removal of the main body of the uterus, leaving the intact cervix in situ. A radical hysterectomy involves removal of the uterus and all surrounding tissues including the adnexae, upper section of the vagina, and regional lymph nodes.

In cases of endometrial cancer, total hysterectomy is the primary treatment modality offered to patients (162). Equally, total hysterectomy is commonly offered to patients with early or invasive cervical cancer, whereas total hysterectomy with bilateral salpingo-oophorectomy is most frequently indicated for ovarian cancer patients (168).

Traditionally, hysterectomies can be undertaken abdominally or vaginally, and, in recent years, laparoscopic surgical methods have become established. An abdominal hysterectomy refers to removal of the uterus via an incision in the lower abdomen whereas a vaginal hysterectomy is characterised by the removal of the uterus via the vaginal canal (189). Various RCTs have been published comparing laparoscopic approaches with open abdominal and vaginal techniques. The largest of such RCTs was the EVALUATE trial which consisted of two parallel trials comparing; 1., laparoscopic and abdominal techniques, and 2., laparoscopic and vaginal (190). The overarching EVALUATE trial recruited 876 women into the laparoscopic and abdominal trial and 504 patients into the laparoscopic and vaginal parallel trial. Overall, the abdominal arm of the trial was sufficiently powered to detect a difference in rates of complication assuming 50% relative reduction from a rate of 9%. Adversely, the vaginal arm of the trial was not sufficiently powered to detect any differences in rates of complications.

2.3.3.1.2 Trachelectomy

In the gynaecology oncology setting, a trachelectomy refers to the surgical removal of the uterine cervix (191). This procedure is employed clinically as a fertility preserving surgical alternative to radical hysterectomy and is applicable to younger patients with early-stage cervical cancer. Broadly, trachelectomies can be categorised as radical or simple; a radical vaginal trachelectomy includes the excision of the adjacent cervical tissue, and vaginal cuff, as well as a lymphadenectomy to assess potential tumour spread. As with hysterectomy techniques, trachelectomies can be undertaken abdominally or vaginally. Various case-control trials have been conducted to verify the safety of both vaginal radical trachelectomy and abdominal radical trachelectomy. A Toronto study of 137 patients observed a 99% 5-year survival rate for patients undergoing vaginal radical trachelectomy (192). A comparable meta-analysis of 485 patients who underwent abdominal radical trachelectomy identified recurrence rates of only 3.8% and observed that only 0.4% of patients had died at 31.6 months median follow-up (193).

2.3.3.1.3 Vaginectomy

A vaginectomy is a procedure performed to remove the vagina (194). Vaginectomies are indicated for women with stage I or II vaginal cancer for whom neoadjuvant radiotherapy was not curative (195). Vaginectomies are commonly undertaken as part of other surgical procedures such as radical hysterectomy or radical vulvectomy (removal of the vulva) and can be classified as simple, partial, radical, or total. Vaginectomies range in extent from a total vaginectomy which refers to the removal of the entire vagina to a simple vaginectomy which involves removal of the vaginal mucosal and underlying muscle layer alone (196). The clinical decision-making process for the selection of appropriate vaginectomy procedure incorporates information on the size, location, and multifocality of the primary lesion. A small study by Jain et al was conducted on 11 vaginal cancer patients who underwent radical vaginectomy to assess disease-free survival and overall survival at 12 months (197). The study reported 88.9% disease-free survival and 100% overall survival, and thereby concluded that stage I and II vaginal cancer patients can be managed judiciously by initial surgery.

2.3.3.1.4 Vulvectomy

Vulvectomy refers to a surgical procedure to remove all, or part, of the vulva (198). A simple vulvectomy is defined by removal of the entire vulva as well as the inner and outer labia (198). In some simple vulvectomy procedures, concurrent removal of the clitoris is also indicated. A complete radical vulvectomy denotes removal of the entire vulva and accompanying deep tissues, inclusive of the clitoris (198). Historically, radical vulvectomy was indicated as the gold standard treatment for any stage of invasive carcinoma of the vulva, however the procedure is accompanied by high rates of morbidity and post-operative complications (199). Therefore, in most large centres, traditional radical vulvectomy methods have been replaced by the so-called triple-excision and primary lesions are primarily managed by radical wide local excision (200).

2.3.3.1.5 Wide local excision

Wide local excision describes the removal of an area of cancerous cells as well as the bordering healthy tissue surrounding the tumour (201). Wide local excision is offered to patients early-stage vaginal and vulval cancers; for vulval cancer patients' surgery is the mainstay of treatment whereas for vaginal cancer patients' surgery is offered in scenarios where alternate therapies were non-curative (196, 200). Previously, radical vulvectomy was indicated for stage I/II vulval cancer patients however wide local excision was introduced to decrease incidence of vulvectomy associated morbidity and complications. A meta-analysis by Hacker et al summarised the results of 11 studies comparing the two techniques and observed no significant increase in mortality rates or disease recurrence for patients undergoing wide local excision (202).

2.3.3.1.6 Conisation

Conisation is a surgical procedure which can be employed to treat early-stage cervical cancer (203). Various methods of conisation exist including cone biopsy and loop electrosurgical excision procedure (LEEP). Typically, LEEP is the preferred method for removal of cervical cancer cells and involves use of a low-voltage electrified wire to remove any abnormal tissue observed during colposcopy (204). One retrospective study analysed data from 131 cervical cancer patients with stage IA2-IB1 disease who underwent LEEP prior to radical hysterectomy (205). This study demonstrated that cervical cancer patients with a depth of invasion of 5mm or less and an endocervical resection margin were able to be characterised as low risk for parametrial invasion and are therefore suitable for LEEP.

2.3.3.2 Radiation therapy

External beam radiation therapy and brachytherapy techniques have previously been described above.

For endometrial cancer patients, IMRT/VMAT techniques are recommended to reduce associated toxicity. Indeed, the PORTEC-3 and GOG-258 trials independently investigated the use of extended field radiotherapy with chemotherapy using IMRT/VMAT techniques and concluded an optimal prescribed dose of 45 to 50.4 Gy in 25-28 fractions administered over a 5-week period (206). Additionally, the BGCS indicate an integrated or sequential EBRT boost for patients with residual lymph node disease, sites of extracapsular nodal spread, and/or positive lateral resection margins as observed on CT-scan (162). The indicated total boost dosage is 55-65 Gy EQD2.

For cervical cancer patients, the BGCS recommend use of pelvic intensity modulated radiotherapy to deliver EBRT as well as use of an appropriate image guided radiotherapy programme (168).

Concomitant intracavity brachytherapy is also indicated. Typically, IMRT techniques are favoured over traditional 3D conformal EBRT techniques owing to the significant reduction in the volume of irradiated tissue and subsequent reduction in treatment related morbidity. According to current guidelines, a total dose of 45-50 Gy using 1.8-2 Gy per fraction is indicated.

Adjuvant radiation therapy is primarily indicated for vulval cancer patients with lymph node involvement confirmed histologically after surgical resection (183). The Gynaecological Oncology Group (GOG) performed various studies during the 1980s-1990s to confirm the benefit of radiation therapy for patients with > 2 lymph node involved, or for patients with > 1 lymph node involvement and extracapsular spread (207). Traditionally, indicated doses of IMRT/VMAT range from 45 Gy to 50 Gy delivered in 25 fractions for vulval cancer patients with inguinal and pelvic node involvement

(183). One published study identified reduced rates of recurrence, however, when doses of 56 Gy were utilised (208).

Radiation therapy is indicated as the standard treatment for patients with vaginal cancers (209). EBRT is usually offered in conjunction with brachytherapy, and the superiority of this combination treatment has been demonstrated in several published studies (210). Generally, vaginal cancer patients are administered 45-50 Gy delivered to the pelvis using IMRT/VMAT techniques (211).

Intracavity brachytherapy is indicated for women with cervical or endometrial cancers and is characterised by the use of an applicator to deliver the radioactive source into an existing body cavity (212). Intracavity brachytherapy allows the delivery of a high radioactive dose to the affected tissue whilst sparing the neighbouring bowel and rectum tissues. For women with locally advanced cervical cancer, intracavity brachytherapy is an integral component of standard management. A study by Han et al utilised the Surveillance, Epidemiology and End Results (SEER) database to conclude that the use of brachytherapy for locally advanced cervical cancer was associated with higher overall survival and cause-specific survival (213). Contrastingly, intracavity brachytherapy, or vaginal vault brachytherapy, is recommended for stage I endometrial cancer patients who are unsuitable for surgical management (214).

2.3.3.3 Systemic therapy

Common platinum-based chemotherapy treatments employed for the treatment of gynaecological cancers include cisplatin and carboplatin (215). Oftentimes platinum-based chemotherapies are administered in combination with paclitaxel, a taxane which prevents cell division (216). The mechanism of action of platinum agents involves the platinum compound entering the cell and binding to DNA (217). This binding to DNA, forming platinum-DNA adducts, interferes with DNA replication, and initiates a DNA-damage recognition response, and cell apoptosis.

Platinum-based chemotherapy, in combination with paclitaxel, is recommended in the adjuvant setting for the majority of ovarian cancer patients (218). Concomitant platinum-based chemotherapy and radiation therapy is also mandated for cervical cancer patients with locally advanced or advanced disease, or in those patients with adverse prognostic factors (168). Similarly, for high-grade endometrial cancer patients, concurrent or sequential platinum-based chemotherapy and paclitaxel is recommended as standard management along with radiation therapy (162).

Cisplatin is also recommended for vaginal and vulval cancer patients; for stage II-IV vaginal cancers in combination with paclitaxel and for those vulval cancer patients with low performance status not medically fit for surgical management (183, 219). In such patients, cisplatin is administered with fluorouracil (5-FU), an antimetabolite drug which prevents formation of DNA.

Bevacizumab is a targeted therapy which is utilised in the treatment of various cancers (220, 221). The medication, also known as Avastin, functions as a monoclonal antibody to block angiogenesis, or the development of new blood vessels. Angiogenesis is prevented through inhibition of the vascular endothelial growth factor A (VEGF-A), a protein which stimulates this process in a number of diseases including cancer. Bevacizumab is offered in the maintenance setting for advanced stage ovarian cancer patients after completion of adjuvant chemotherapy (157).

2.3.3.4 Treatment by FIGO stage or risk-group

2.3.3.4.1 Ovarian Cancer

The BGCS guidelines recommend that any ovarian cancer patient diagnosed with early-stage disease (defined as FIGO stage I or II cancer) should primarily be offered surgical resection (157). Adequate primary surgery, in the non-fertility sparing setting, usually consists of bilateral salpingo-oophorectomy, total hysterectomy, and biopsy of the peritoneal region including pelvic and bilateral para-aortic lymph node assessment. Lymph node dissection is not warranted in such early-stage settings, owing to the overall low rate of lymph node involvement in such tumours.

Following initial surgical resection, ovarian cancer treatment guidelines stipulate that adjuvant platinum-based chemotherapy should be offered in all cases of early-stage ovarian cancer (FIGO stage I or II) with the exception of low-grade Ia/Ib disease (157). Two published RCTs independently examined the value of adjuvant chemotherapy in early-stage ovarian cancer. The ICON1 study investigated the addition of six cycles of adjuvant single agent carboplatin and observed a significant improvement in relapse-free survival ($HR = 0.65$, 95% $CI: 0.46-0.91$) and overall survival ($HR = 0.66$, 95% $CI: 0.45-0.97$) at four years median follow-up (222). The ACTION trial reported similar findings in a cohort of patients prescribed platinum-based combination chemotherapy (223). A further Cochrane meta-analysis including five large RCTs reported improved overall survival ($HR = 0.71$, 95% $CI: 0.53-0.93$) and progression free survival ($HR = 0.67$, 95% $CI: 0.53-0.84$) in patients receiving platinum-based adjuvant chemotherapy compared to patients who underwent observation alone (224).

For ovarian cancer patients with advanced disease (defined as FIGO stage II-IV) primary debulking surgery is the gold standard treatment in cases where optimal or complete resection appears achievable (157). Patient performance status is a key consideration in the decision-making process and neoadjuvant chemotherapy is indicated for patients with poor performance status for whom debulking surgery is likely to be sub-optimal. Various prospective RCTs have reported non-inferiority of offering neoadjuvant chemotherapy and subsequent debulking surgery and indeed concluded reduced morbidity for patients in the neoadjuvant chemotherapy trial arm (225, 226).

According to current standard of care guidelines, post-operative cytotoxic chemotherapy in the form of carboplatin and paclitaxel should be offered three-weekly for ovarian cancer patients with advanced disease (157). If tolerated, and depending on patient fitness, six cycles should be completed in total. Further targeted therapies can be offered in the maintenance setting and have been demonstrated to increase progression free survival. The ICON7 trial reported improved progression free survival for patients who received 12 months of maintenance bevacizumab following cytotoxic chemotherapy (227).

2.3.3.4.2 Cervical Cancer

For patients with FIGO defined stage IA1 cervical cancer, various guidelines now endorse the use of conisation to achieve negative tumour margins (228, 229). In the UK specifically, LLETZ is the favoured conisation technique. Conversely, radical hysterectomy and bilateral salpingectomy +/- bilateral oophorectomy with bilateral pelvic lymphadenectomy is mandated as the standard management for patients with FIGO stages IA2, IB1 and IB2 cervical cancer (168).

Adjuvant treatment following surgery is recommended for cervical cancer patients with adverse prognostic factors, as elucidated following final postoperative staging (168). Histopathological risk factors deemed as high-risk and requiring further consideration in the treatment decision making process include positive pelvic/para-aortic lymph nodes, parametrial spread, or positive surgical margins. The BCGS guidelines indicate offering adjuvant concurrent chemoradiotherapy to patients with high-risk factors present in specimens of the radical hysterectomy (168). Published evidence concludes that use of concurrent chemoradiotherapy is superior to radiation therapy alone (230).

A variety of histopathological factors are also classified as intermediate risk including presence of lymphovascular space invasion, maximum tumour diameter > 4cm at final pathology, and deep cervical stromal invasion (>1/3). The GOG 92 trial assessed the oncological outcomes of patients with 2 or more intermediate-risk factors after radical hysterectomy and pelvic lymphadenectomy and concluded that patients receiving adjuvant radiotherapy exhibited significantly improved recurrence free survival (231, 232). The results of this trial inform clinical decision making and patients with defined intermediate-risk factors should be considered for adjuvant chemoradiotherapy or close observation.

For patients with locally advanced cervical cancer (FIGO stage IB3-IVA) the BCGS outline gold standard treatment as chemo-radiotherapy consisting of EBRT, intracavity brachytherapy and concomitant chemotherapy with cisplatin (168). One published RCT compared radical surgery and radical radiotherapy treatments for squamous cell patients with FIGO stage IB-IIA disease and identified no survival difference but higher morbidity in patients undergoing a combination of

treatment modalities (233). The results of this trial influenced treatment guidelines where patients who were previously expected to require postoperative chemoradiotherapy are no longer offered combination treatment or surgery. Cervical cancer patients with FIGO stage IB3/IIA disease should therefore be clinically managed avoiding the necessity of combination surgery and postoperative radiation therapy, and definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment strategy (168). Additional radiation boost targeting involved lymph nodes is indicated for cervical cancer patients with locally advanced disease. For patients with stage IIB, IIIA/IIIB or IVA disease, definitive chemoradiotherapy and brachytherapy with an additional radiation boost to the involved lymph nodes is the standard offered treatment.

2.3.3.4.3 Endometrial Cancer

The primary treatment pathway for endometrial cancers involves surgery, and the standard surgical procedure offered to most patients is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff or parametrectomy (162). For premenopausal women with defined low risk disease, hysterectomy or salpingectomy with ovarian conservation can be considered. Safety data for such ovarian conserving surgery is based primarily on retrospective data. One published meta-analysis included studies investigating recurrence free survival in premenopausal endometrial cancer patients with FIGO stage I/II and concluded no adverse impact of ovarian conservation surgery (*RR: 1.1, 95% CI: 0.59-2.10*) (234).

For women who are deemed unfit for standard surgery, vaginal hysterectomy, definitive pelvic radiotherapy, or progestin/aromatase inhibitors may be considered (162). The selection of appropriate non-standard surgical management should be informed by patient characteristics and the preferences of local sites. For patients diagnosed with high-grade or high-intermediate grade endometrial cancers, combination EBRT and intracavity brachytherapy may be offered, and intracavity brachytherapy alone offered for women with low grade disease (235). Equally, 3-6 months of progestin therapy may be considered for women with low grade tumours to allow surgical postponement (236).

Various clinical studies have demonstrated no clinical benefit for adjuvant treatment following initial surgery for women with defined low-risk endometrial cancer (237, 238). For patients with intermediate-risk endometrial cancer, vaginal vault brachytherapy is recommended to reduce the risk of vaginal recurrence after surgery (162). The PORTEC-2 trial randomised 427 women with intermediate risk endometrial cancer to vaginal vault brachytherapy or EBRT and noted similar rates of vaginal and isolated relapse in both groups (239). Longer term follow-up information however

observed a significantly increased late toxicity for women receiving EBRT compared to brachytherapy.

Women with high-intermediate-risk endometrial cancer are recommended adjuvant brachytherapy in cases where no lymphovascular space invasion has been identified following surgical staging of the lymph nodes (162). Where lymphovascular space invasion has been identified, EBRT is advocated. In cases where surgical staging of the lymph nodes has not occurred, adjuvant EBRT is primarily endorsed, although adjuvant chemotherapy can also be offered in cases where substantial lymphovascular space invasion is present.

For patients with high-grade endometrial cancer, either EBRT with concurrent and adjuvant chemotherapy, or sequential chemotherapy and radiotherapy is proposed as standard management (162). It is well established that EBRT is associated with reduced risk of recurrence when used in standard of care settings for endometrial cancer patients with stage III disease. The PORTEC-3 trial randomised patients to receive concurrent and adjuvant additional chemotherapy compared to EBRT alone and demonstrated a statistically significant 5% overall survival benefit at 5 years and 7% failure free survival benefit in the combined treatment group (240). Postoperative carboplatin-paclitaxel chemotherapy administered in the adjuvant setting is associated with improved oncologic outcomes irrespective of EBRT use.

2.3.3.4.4 Vaginal Cancer

As primary vaginal cancer is a rare disease, there currently exists no official treatment guidelines for clinical management (241). General principles which incorporate clinical characteristics such as disease, location, lesion size and clinical staging have, however, been developed to aide clinical decision making.

FIGO stage I and II vaginal cancers may be treated surgically when the tumour is located in the apex, the upper posterior, or lateral portions of the vagina (211). For stage I vaginal cancers, total hysterectomy and radical vaginectomy is indicated along with accompanying lymph node dissection, except for in cases where small superficial lesions are observed (211). Wide local excision can be employed in such cases along with intracavity adjuvant radiation therapy. Early-stage lesions located in the middle or distal portions of the vagina are usually treated with radiation therapy alone.

Traditionally, surgery was the primary therapeutic modality for vaginal cancers however, in recent years, radiation therapy has largely replaced this (211). Radiation therapy has become favoured owing to anatomical constraints of vaginal surgery, and the inability to achieve negative surgical margins without radical exenteration procedures. EBRT in combination with brachytherapy is

indicated for FIGO stage II vaginal cancers delivered in a combined dose of 70-80 Gy. Additionally, a small prospective study observed that 27% of stage II vaginal cancer patients achieved complete response when treated with 3 cycles of neoadjuvant paclitaxel and cisplatin presenting evidence that neoadjuvant chemotherapy followed by radical surgery may provide an alternative to radiation therapy (242).

Radiation therapy is the standard treatment for patients with stage III-IV vaginal cancers (211). For women diagnosed with stage III disease, pelvic EBRT is usually administered with a side wall boost dose to yield a total tumour dose of 75-80 Gy. Chemotherapy is often administered in conjunction with such radiation therapy (211). A similar management approach is usually employed for stage IV disease with standard management comprising a combination of interstitial radiation therapy, intracavity radiation therapy and EBRT, followed by an interstitial or intracavity implanted boost to achieve a total tumour dose of 75-80 Gy. Additionally, a lateral sidewall boost of 55-60 Gy is administered.

2.3.3.4.5 Vulval Cancer

Primary surgery with curative intent usually forms the basis of treatment for vulval cancers (183). Small tumours (FIGO stage Ia) can be managed utilising excision, provided that negative margins are achieved. Management of FIGO stage Ib vulval lesions is determined by the location of the tumour; where tumours are located laterally of the midline, wide local excision can be employed. Contrastingly, in cases where the tumour is peri-clitoral or located in the posterior region of the vulva, anterior or posterior vulvectomies are indicated, respectively. Large or multifocal tumours necessitate a radical vulvectomy.

Stage II and III vulval cancers are managed ensuring achievement of negative surgical margins (183). In cases where the anus is involved, neoadjuvant or concurrent chemoradiotherapy may be offered to reduce tumour volume and maintain faecal continence. When disease is observed in the sentinel lymph nodes, additional treatment is mandated usually in the form of radiation therapy (183). Radiation therapy is also favoured in the adjuvant setting for patients with high-risk disease with >2 lymph node involvement or extracapsular spread. Principally, surgery is rarely employed for stage IV tumours and palliative treatment is favoured.

The prescription of neoadjuvant chemotherapy is usually limited to vulval cancer patients with poor performance status, or for those with large primary tumour volume who require downstaging of tumour prior to conservative surgery or radiation therapy (183). The use of neoadjuvant chemotherapy in this setting has been explored in small case series alone. Recent studies investigating the use of neoadjuvant infusion 5-FU with cisplatin for patients with locally advanced

vulval cancer yielded responses ranging from 20-100% (243, 244). Traditionally, adjuvant chemotherapy is not routinely prescribed for vulval cancer patients.

2.3.4 Adverse effects of gynaecological cancer therapies

2.3.4.1 *Lymphoedema*

Lower limb lymphoedema is well established as one of the most debilitating side effects of surgical and radiotherapy treatment for gynaecological cancers (245). Lower limb lymphoedema is defined as swelling of the leg(s) and typically presents in the first 12 months following cancer treatment. The condition is most prevalent in vulval cancer patients (36%), however is also commonly described by cervical cancer patients undergoing radiation therapy or surgical removal of the lymph node system (245). Published literature reports that approximately 10% of all gynaecological cancer patients are diagnosed with lower limb lymphoedema, and a further 15% of patients experience symptomatic leg swelling without receipt of an official lymphoedema diagnosis (246).

2.3.4.2 *Sexual dysfunction*

The numbers of gynaecological cancer survivors continue to increase as novel diagnostic and treatment techniques emerge. Treatment associated survival gains are, however, often accompanied by side effects, and diminished sexual functioning is one of the most common issues experienced in gynaecological cancer populations (247). Commonly arising sexual functioning issues include loss of sexual desire, dyspareunia (or painful intercourse), loss of sensation in the genital area, and loss of orgasmic functioning (248).

For endometrial cancer patients with early-stage disease, surgery is indicated as the optimal treatment option. A study by Onujiogu identified sexual dysfunction in 89% of stage I-IIIa endometrial cancer patients undergoing primary surgical treatment (249). Sexual dysfunction was observed over the study period of 1-5 years post-surgery and pain was the most commonly reported symptom. Conversely, for higher-risk endometrial patients, adjuvant radiation therapy or chemotherapy is typically recommended. The PORTEC-2 study investigated adverse symptoms associated with vaginal brachytherapy compared to EBRT but concluded that participants in both arms experienced significantly more vaginal dryness, coupled with lower sexual interest, activity and enjoyment when compared with an age-matched control cohort (250).

Radical hysterectomy is associated with significant sexual dysfunction for cervical cancer patients (251). In the short-term, symptoms can manifest as orgasmic issues, vaginal shortening, dyspareunia, genital numbness and sexual dissatisfaction (252). Longer term symptoms of sexual dysfunction include loss of sexual interest, lymphoedema, genital numbness and insufficient lubrication. Genital numbness is the most prevalent of symptoms with 71% of cervical cancer

patients experiencing such consequences post-surgery (253). Similarly, for cervical cancer patients undergoing EBRT or vaginal brachytherapy, common toxicities include stenosis, or narrowing of the vaginal canal, vaginal shortening, vaginal atrophy, vaginal fibrosis, and dyspareunia (254, 255). Published evidence observed greater sexual dysfunction for patients undergoing primary or adjuvant radiotherapy compared to surgery alone (256).

Primary treatment for ovarian cancers usually consists of hysterectomy including oophorectomy. Removal of the ovaries results in significant hormonal alterations including induction of the menopause for younger otherwise pre-menopausal women (257). Symptoms of diminished sexual functioning for these women comprise significantly decreased sexual pleasure and desire (258). Equally, vaginal dryness and increased dyspareunia are reported more often in ovarian cancer patients and survivors compared to healthy women (259).

Women with vulval cancers are typically treated with radical surgery which can result in significant anatomical alteration and, in turn, impact sexual functioning. Such physical alterations classically include vaginal shortening, numbness, removal of the clitoris, and changes to tissue quality (260). Lymphoedema is also commonly experienced by vulval cancer patients undergoing lymphadenectomy and negatively impacts sexual quality of life (261). Radiation therapy has been demonstrated to negatively affect arousal and orgasm ability (262).

Vaginal cancer patients and survivors suffer significant issues related to sexual functioning including vaginal shortening and dryness following radiation therapy (263, 264). Additionally, vaginal numbness and loss of sexual pleasure is also commonly observed, as well as vaginal fibrosis. Women with vaginal cancers also commonly report dyspareunia.

2.3.4.3 Urinary functioning

Dysfunction of the lower urinary tract is frequently observed in gynaecological malignancies, manifesting both as a secondary symptom of the lesion itself and as a longer-term effect of radiation and surgical therapies (265). Urinary incontinence is widely accepted as the most notable adverse effect of gynaecological cancer treatments with one published study indicating that the prevalence of this symptom post-surgery was 52.4% (266). Further urinary dysfunction which can occur following radical surgery, radiotherapy or chemotherapy includes difficulties related to voiding (267).

2.3.4.4 Bowel functioning

Bowel dysfunction commonly occurs secondary to the denervation process of radical hysterectomy but is more prevalent in gynaecological cancer patients undergoing radiation therapy. Common bowel symptoms include diarrhoea, defecatory urgency, pain, bleeding, and faecal incontinence.

One published study investigated bowel symptoms after radiation therapy in a cohort of 217 gynaecological cancer patients (268). This study reported that 40.7% of the population experienced defecatory urgency and ~15% reported faecal incontinence. Additionally, usual loose stools and diarrhoea were reported by 13.5% and 5.1% of patients, respectively. The results of this study were in line with a similar larger study of 1029 gynaecological cancer patients which also reported significant impact on quality of life for those patients experiencing bowel dysfunction (269).

Additionally, some symptoms of radiation associated bowel toxicity develop after a longer latency period of > 6 months (270). Such symptoms are referred to as delayed radiation enteropathy and can present clinically as altered intestinal transit, or the time taken for digested food to pass through the intestines, malabsorption of nutrients, and/or dysmotility where the muscles of the intestinal wall become uncoordinated. One previously published study of cervical cancer patients specifically estimated the incidence of severe toxicity to lie around 10% for patients undergoing chemoradiation therapy (271).

2.3.4.5 Infertility

The preservation of fertility for women of reproductive age with gynaecological cancer is a complex process (272). Both surgical and gonadotoxic chemotherapy and radiation treatments affect fertility yet published evidence suggests that many women are not informed about the risks of infertility nor are offered fertility preservation prior to commencement of treatment (273). A study of 51 cervical cancer patients and 50 age-matched healthy women reported the psychological impact of infertility, presenting that the reproductive concerns of these women were associated with poorer quality of life and increased cancer-specific distress (274). Around 20% of gynaecological cancer cases occur in women under the age of 40 years, and often these patients have not completed parity when diagnosed (275).

2.3.4.6 Induced menopause

One of the consequences of utilising chemotherapy or radiation therapy to treat gynaecological cancer is loss of ovarian function (276). For younger gynaecological cancer patients, such loss of ovarian function results in early menopause, or iatrogenic cessation of the menses (277). These patients often suffer with intense symptoms of the menopause including hot flushes, night sweats, sleep, and mood disturbances, as well as genitourinary issues such as decreased libido, and pain. A study by Wright et al estimated that around 30-40% of all gynaecological cancer patients experience menopausal symptoms or undergo the menopause prior to the time of anticipated natural menopause.

2.3.4.7 Pelvic insufficiency fracture

Pelvic insufficiency fractures are characterised as stress fractures which occur when normal levels of stress are applied to a pelvic bone with decreased mineralisation and elastic resistance (278).

Previously, pelvic insufficiency fractures were understood to be a rarer side effect of radiation therapy however recent studies have estimated the incidence to be between 11.1%-36.9% for gynaecologic cancer patients at 2-years post-treatment (279, 280).

2.3.4.8 Neuropathy and lumbosacral plexopathy

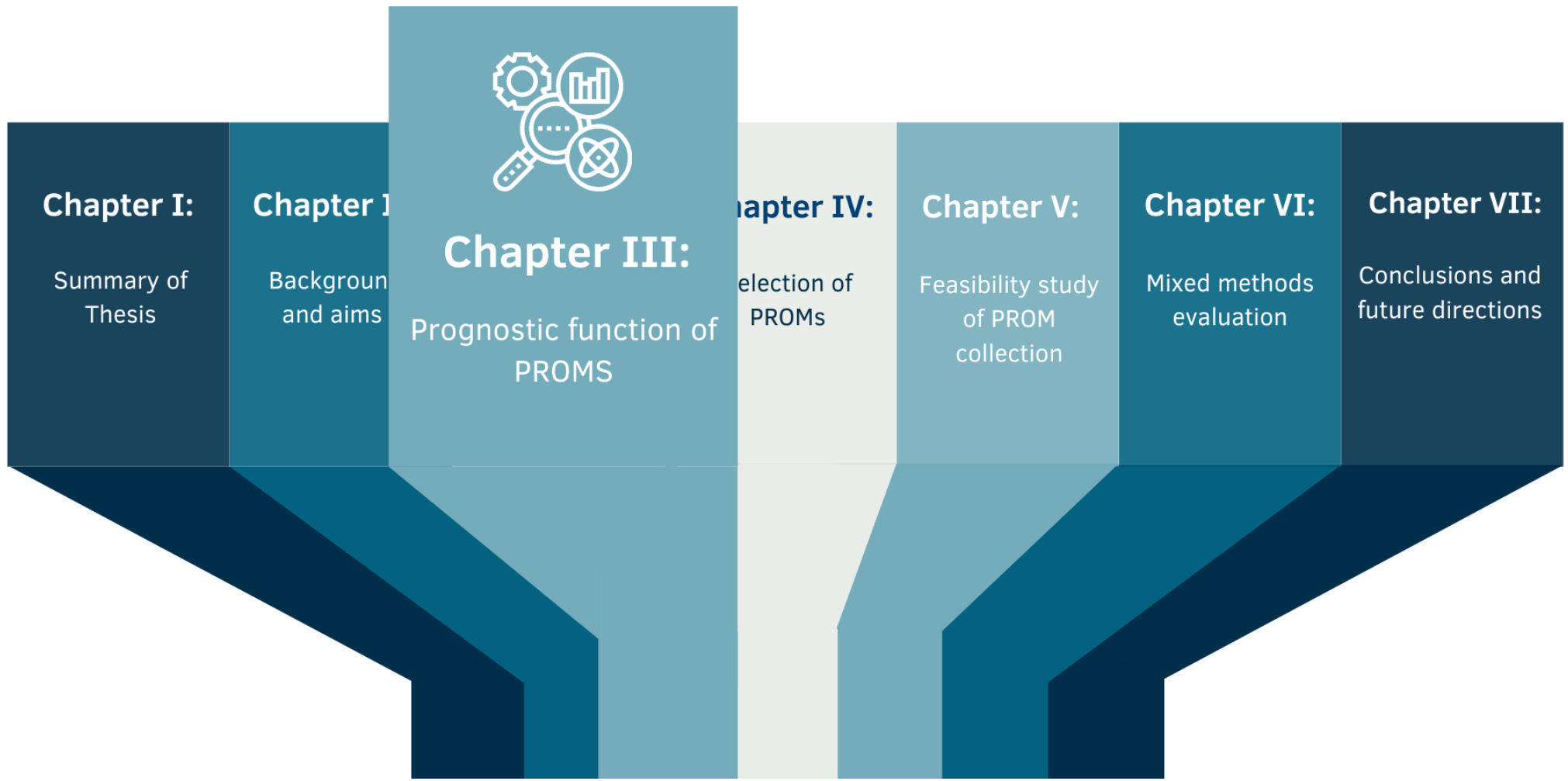
Peripheral neuropathy is a common side effect of chemotherapy-based treatments for gynaecological cancers. Peripheral neuropathy can present in two modes; either as sensory peripheral neuropathy which is characterised by numbness, tingling, cramps, and pain in the extremities, or as motor peripheral neuropathy which involves muscle wasting, weakness, fasciculation, or cramps (281). The published ROGY survivorship care study estimates that between 50-60% of ovarian cancer patients undergoing adjuvant chemotherapy experience peripheral neuropathy (281). Conversely, for ovarian cancer patients with recurrent disease the study reported 70-80% of patients experiencing peripheral neuropathy.

Lumbosacral plexopathy is typified by inflammation and/or damage to the nerve bundles located in the lumbar and sacral vertebrae regions (282). Symptoms of this rare but complex radiation-induced complication include pain, muscle weakness, and sensory deficits. Incidence of the complication ranges from 0.3-1.3% with a long latency period between the completion of radiation therapy and onset of symptoms (283).

Chapter III:

Prognostic function of PROMs

This chapter explores the prognostic function of patient-reported outcome measures in terms of oncological outcomes, and provides a rationale for the implementation of routine clinical collection in cancer settings.



3. Chapter III: Prognostic function of PROMs

The ensuing chapter presents the rationale, methods, results, discussion, and conclusions for the first project of this thesis. This project aimed to explore any potential prognostic role of PROMs, in malignancies of the pelvic abdominal cavity. A systematic review of the literature was undertaken, and the findings of this study are published in the BMC Health and Quality of Life Outcomes journal (Appendix I) (Moss, Aggarwal, *et al.*, 2021).

3.1 Rationale

In the context of cancer, the routine use of PROMs is limited primarily to the research and randomised control trial (RCT) setting, where PROMs are used to monitor health status and quality of life before, during and after experimental treatments. PROMs are employed in such settings to assess whether the survival benefits of a specific treatment may outweigh any potential side effects or for choosing between treatment options which offer similar survival benefit (22, 23, 24).

Empirical evidence exists, however, to support the use of PROMs in the routine cancer clinical setting. For example, compiled PROM data can be utilised to inform patients about the benefits and side effects of different treatment regimens. Such treatment decision making process can be undertaken as part of shared decision making (between the clinical teams and the patient), or by the patient individually, utilising patients' decision aids (284). Note, patient decision aids are defined as "evidence-based tools designed to assist patients with making specific and deliberate choices among healthcare options" (285).

Moreover, various evidence presents a rationale for the routine clinical use of PROMs as part of patient management, particularly for patients with longer-term conditions such as cancer. Baseline and subsequent follow-up collection of PROMs in such conditions can be utilised to assess disease progression and monitor the effects of treatment (286). One study by Valderas *et al* also presented data to support the use of PROMs to identify vulnerable patients and facilitate continuous evaluation of care quality (287).

From the clinician perspective, less obvious benefits of routine PROM administration include improved patient memory, recall, and articulation of symptom burden (288). Equally, PROM tools can be used to highlight symptoms that patients may otherwise had not thought to raise for discussion with their clinical teams. The use of PROMs regularly throughout patient's cancer journey may also assist with ensuring that patients feel well cared for, and PROMs can be employed as a structured basis for patient-clinician discussion during consultation.

Administration of PROMs may also be used to identify poor performance and poor clinical practice within healthcare systems. In such cases, outliers, or lower than anticipated improvements in PROM scores, may be useful for developing improvement programmes within clinical practice.

Despite comprehensive evidence conferring the benefit of the routine clinical use of PROMs, there exists a paucity of data on the use of PROMs to improve patient health outcomes. Some emerging evidence suggests a potential role for PROMs as independent prognostic tools which, when used alongside clinicopathological information, may provide clinicians with a more valid and comprehensive understanding of patient disease. For example, a published study by Geerse et al evaluated the addition of a patient-reported distress score, used in combination with clinical factors, to predict 1-year survival in lung cancer patients (289). This study observed a prognostic value for the distress score and suggested that collection of such a tool may assist in the identification of lung cancer patients at risk of poor survival outcomes. Equally, a study of 282 advanced melanoma, non-small-cell lung, colorectal and breast cancer patients investigated the association between PROMs and both overall and hospitalisation-free survival (290). This study identified a strong prognostic association between physical function, fatigue, depression, anxiety, and pain with overall and hospitalisation-free survival.

This first study therefore sought to systematically review the literature to determine current understanding of the potential prognostic role of PROMs, with specific reference to tumours of the pelvic-abdominal cavity. The whole anatomical region of the pelvic-abdominal cavity was selected to ensure inclusion of sufficient appraisable data for this purpose. Studies were critically assessed to identify any measurable oncologic benefit and are described using a narrative presentation.

3.2 Methods

3.2.1 Search Strategy and Inclusion Criteria

The research question, search strategy, and inclusion and exclusion criteria were developed prior to commencement of literature searching in April 2020. Relevant studies were identified by conducting searches of Medline (Pubmed) and Ovid Gateway (Embase and Ovid) using the listed search terms from inception until April 2020. A comprehensive set of search terms was compiled and is included below:

Kidney cancer or renal cancer* or kidney neoplasm* or renal neoplasm* or prostate cancer* or prostatic cancer* or prostate neoplasm* or prostatic neoplasm* or testicular cancer* or testis cancer* or testicular neoplasm**

Bladder cancer or bladder neoplasm* or bladder tumor* or bladder tumour* or urinary bladder cancer* or urinary bladder neoplasm* or malignant tumor of urinary bladder**

Cervix cancer or uterine cervical cancer* or cervical neoplasm* or cervix neoplasm* or uterine cervical neoplasm**

Vagina cancer or vagina* neoplasm**

Ovary cancer or ovarian cancer* or ovary neoplasm* or ovarian neoplasm**

Vulva cancer* or vulva* neoplasm**

Endometr cancer or endometr* neoplasm* or uterine neoplasm**

*Fallopian tube cancer or fallopian tube neoplasm**

Hepatic cancer or liver cancer or hepatocellular cancer or hepatic neoplasm or hepatic neoplasm* or hepatocellular neoplasm**

Gastric cancer or stomach cancer* or gastric neoplasm* or stomach neoplasm**

Colon cancer* or colon* neoplasm**

Pancreas cancer or pancreatic cancer* or pancreas neoplasm* or pancreatic neoplasm**

Rect cancer* or rectal tumour or rectal tumor or rect* neoplasm**

Anal cancer or anal neoplasm* or anus cancer* or anus neoplasm**

Patient reported outcome or patient reported outcome measurements or PROM or patient satisfaction or PREM or PRO or outcome measure or outcome assessment or outcomes research or outcome study*

Hrqol or health related quality of life or health-related quality of life or life quality or quality of life or QoL

((Survey or survey) and questionnaire) or respond or survey method* or assessment or report or relate* or apprais**

exp Survival Rate/ or exp Disease-Free Survival/ or exp Survival/ or exp Progression-Free Survival/ or survival

After searching, the list of returned articles was further filtered to include only articles published in the English language and studies referring to humans alone. Reference lists of included articles were also checked for additional relevant literature.

The full inclusion and exclusion criteria are presented below in Table 6. The following inclusion criteria was utilised: a randomised control trial, an observational study, or an original article, written in the English language, and investigating the oncological outcomes associated with PROMs in patients with urological, gynaecological, colorectal, pancreatic, gastric, or hepatic tumour types. Commentaries, author's replies, reviews, supplements, editorials, and systematic reviews were excluded. Studies that included patients with cancers other than pelvic abdominal tumours were included on the condition that the relevant pelvic abdominal cancer data could be isolated.

Table 6: Inclusion and exclusion criteria for screening

<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>
Peer reviewed paper	Non full text articles
Published at any time before April 2020	Non-English papers
	Systematic Reviews
<i>Quantitative analyses</i>	
Includes participants:	
Patients diagnosed with:	Studies in which data pertaining to any of the included tumour types could not be isolated
- Any urological cancer	
- Any gynaecological cancer	
- Any colorectal cancer	
- Any gastric cancer	
- Any hepatic cancer	
- Any pancreatic cancer	
Disease stage: any	
Treatment regimen: any	
Demographic: any	
<i>Quantitative studies</i>	
Design:	
- Randomised control trial	
- Prospective cohort	
- Non-randomised control trial	
- Cross sectional	
Variables examined:	
- Prognostic potential of PROMs	
- Specific QoL instruments with prognostic potential	

PROMs: patient-reported outcome measures, QoL: quality of life

All duplicates were removed, and articles were reviewed by title, abstract and full text by the first author (CM). A second author (MVH) subsequently reproduced the results of the search strategy before independently undertaking screening of all articles included for full text review. In case of disagreement, a third independent reviewer (TGU) was consulted to confirm the final list of included studies. Management of the screening process occurred using Microsoft Excel.

3.2.2 Quality Assessment

Initially, the quality of each study was assessed by CM using quality assessment tools developed by the Joanna Briggs Institute (JBI) (<http://joannabriggs.org/research/critical-appraisal-tools.html>). The JBI have developed various tools for assessing the quality of quantitative studies that are appropriate for use in systematic reviews to appraise questions of aetiology and risk. The purpose of such appraisals is to broadly assess the methodological quality of a study and to determine the extent to which each study addresses the possibility of bias in its design, conduct and analysis. Owing to the varying design of the studies included in this review, JBI critical appraisal checklists for cohort studies, RCTs and case series were utilised. The appraisals are included as appendices (Tables 1-3, Appendix II). Following critical appraisal by CM, a second author (MVH) independently assessed the quality of each included study using the JBI critical appraisal tools. Each of the studies were subsequently discussed to identify any differences in opinion with consultation from a third author (TGU).

3.3 Results

As detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 5), the search strategy identified 2191 articles. Following the removal of 24 duplicates, and using the inclusion criteria outlined above, 2167 articles were screened by title. A further 228 records subsequently underwent abstract review before 43 were assessed based on the full text. Overall, 21 articles were deemed suitable for inclusion.

Of the 21 included studies, seven were RCTs and 14 were observational in design (11 cohort studies, and three case series). The articles were published between 1997 and 2018 and included sample sizes ranging from 47 to 2603 patients. Seven of the studies were conducted on patients with pancreatic cancer; six on patients with a diagnosis of colorectal cancer; five on prostate cancer patients; four on urological cancers (including bladder and renal cancers); three on gynaecological cancers and two on gastric cancer patients. Although the studies were conducted worldwide, a large proportion (10 out of 21 studies) were published in the United States. The treatment setting of each included study also differed; five of the studies included patients undergoing chemotherapy regimens, three were conducted in the surgical setting, one study included survivors only, and two studies included patients receiving targeted therapy or hormonal therapy/radiotherapy. Full details of each of the included studies, including the PROM instruments used, the aims of each study, and a summary of findings are presented in Table 7.

5. Figure 5: PRISMA flow diagram of screening process

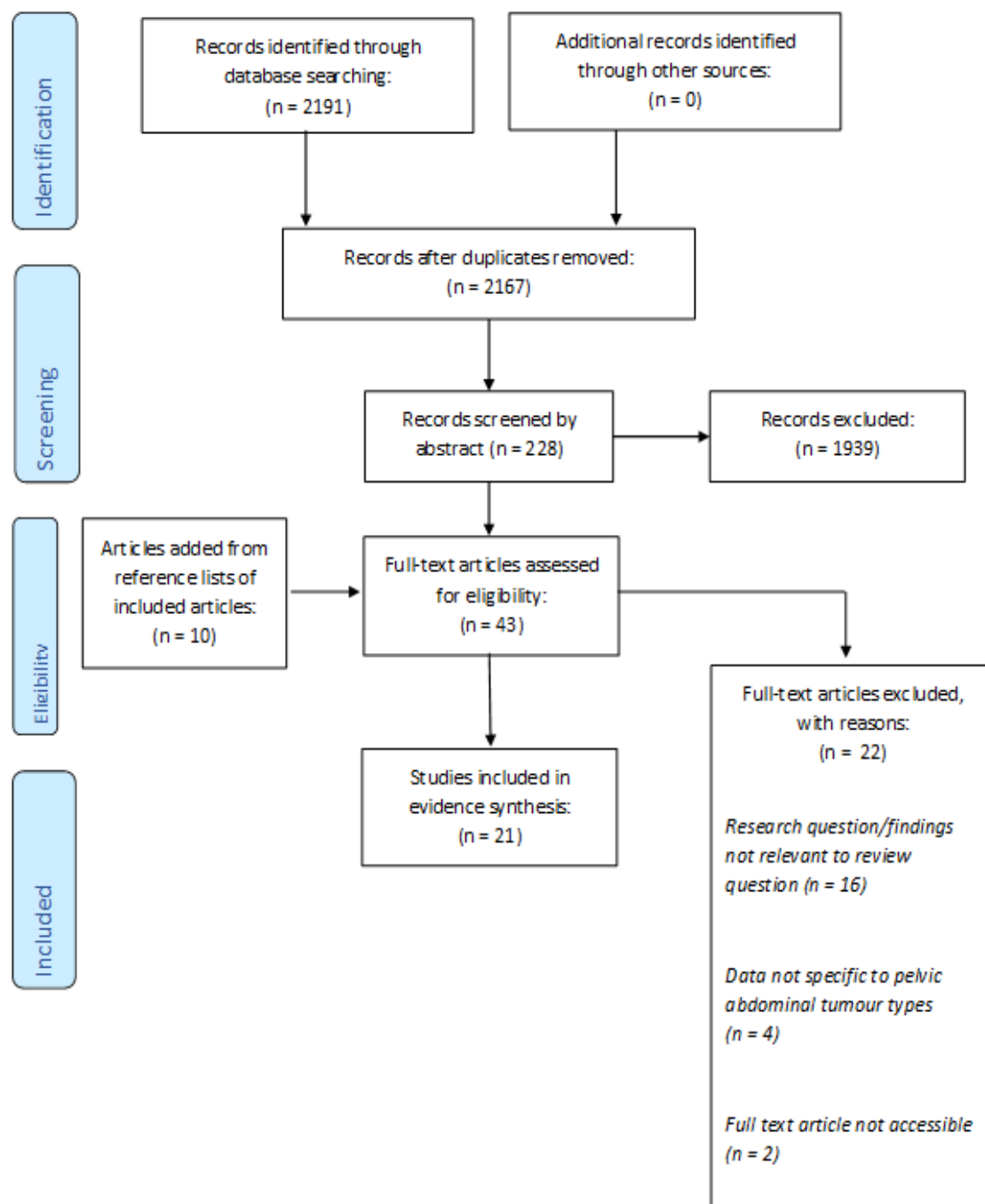


Table 7: Descriptives of included studies

ID	Ref	Author, (Date of Publication)	Study Population: No. of Participants, Age (Mean (S.D.)) and Sex (n(%))	Tumour Type, Country of Study	PROMs used	Study Aims	Statistical Analysis, Covariates	Summary of Findings
1	(291)	de Rooij et al (2018),	N= 2457; Age: 68.1 (10.1); M: 1457 (59) F: 1000 (41)	Colorectal, Urological, Gynaecological The Netherlands	EORTC QLQ-C30, Hospital Anxiety and Depression Scale (HADS)	Identification of subgroups of cancer survivors with realistic, pessimistic or optimistic illness perceptions (IPs) relative to prognosis at time of questionnaire. Assessment of HRQoL and survival associated with these subgroups.	Multivariate Cox proportional Hazards regression models Clinical/demographic characteristics	Functioning and global QoL were higher and symptom burden lower in those with optimistic illness perceptions compared with realistic IPs (all P < 0.01) Functioning was lower, and symptoms were higher in those with pessimistic IPs compared to those with realistic IP (all P < 0.01) All-cause mortality higher in survivors with pessimistic IPs compared with those with realistic IPs (HR: 1.52, 95% CI (1.27-1.84))
2	(292)	Graham et al (2018),	N= 68; Age: 64.15; M: 53 (77.9) F: 15 (22.1)	Renal United States	Edmonton Symptom Assessment System (ESAS)	Assessment of whether ESAS measured at baseline can provide prognostic information for patients receiving standard first-line	Multivariate Cox proportional Hazards regression models, Known prognostic	In multivariate analysis, higher baseline symptom burden was associated with inferior overall survival (HR: 1.21, 95% CI (1.01-1.44) for each 10-unit increase in the ESAS total score when controlling for the mskcc risk

						sunitinib for metastatic renal cell carcinoma (mRCC)	indicators of mRCC	group and 1.240 ($p = 0.019$) for each 10-unit increase when controlling for the imdc risk group. Baseline symptom burden, as measured by ESAS, provides modest degree of prognostic information independently of other widely used prognostic factors.
3	(293)	Baekelandt et al (2016),	N= 66; Age: 68 (34-83); M: 20 (30.3) F: 44 (69.7)	Pancreatic Norway	EORTC QLQ-C30, EORTC QLQ-PAN26, Edmonton Symptom Assessment System (ESAS)	Assess the prognostic significance of pretreatment HRQoL and symptom scores on survival in patients with resectable pancreatic ductal adenocarcinoma	Multivariate Cox proportional Hazards regression models Clinical/demographic characteristics	Six reported variables with $P < 0.20$ eligible for multivariate model. After stepwise backward selection only cognitive function remained in model. Based on results of prognostic impact of PROs on survival, patients divided into 2 groups: those with high vs those with low cognitive function. Hazard ratio for death (HR 3.5, 95% CI (1.7-7.3) higher in patients with low cognitive function compared to higher cognitive function.

4	(294)	Moningi et al (2015),	N= 110; Age: NI; M: NI F:NI	Pancreatic United States	EORTC QLQ-PAN26	Examine associations between QoL as they relate to self-reported symptoms, clinical characteristics and performance status.	Pearson's Chi-squared Test	Patients with lower performance status measured by both ECOG and KPS had worse QoL scores: pain, digestive symptoms, cachexia, ascites (P < 0.05). More aggressive symptom management may result in improved PFS and better outcomes for pancreatic patients.
5	(295)	Bingener et al (2015),	N= 431; Age: 69.0 (11.2); M: 219(50.8) F: 212 (49.2)	Colorectal United States	Symptom Distress Scale, 5-item Quality of Life Index	Investigate whether deficits in preoperative QoL scores are associated with surgical outcomes such as 30-day morbidity. Determine whether change in QoL postoperatively associated with morbidity.	Stepwise logistic and linear models Demographics	Changes from baseline to day 2 QoL indicators, including concentration (OR1.27 (1.00–1.61) p =0.049), appearance (OR 1.38 (1.02–1.87) p=0.037), breathing (OR 1.50 (1.02–2.21), p=0.038) significantly associated with early complications. Changes from baseline to day 14 in 'activities', 'daily living' and 'total QLI' were also associated with early complications. Using stepwise logistic model, the variables significantly associated with having any early complications (yes/no) were age, ASA III and change in 'activity' from baseline to day 14. Significant predictors for

								being readmitted to the hospital within 2 months were baseline pain distress severity and changes from baseline to day 2 in fatigue. Also associated with readmission were changes from baseline to postoperative day 14 in 'daily living' and outlook.
6	(296)	Quinten et al (2013),	N= 2603; Age: NI; M: NI F: NI	Colorectal, Urological, Gynaecological, Pancreatic Belgium	EORTC QLQ-C30	Investigate the relative contribution of different HRQoL domains as prognostic for separate cancer types	Multivariate Cox proportional Hazards regression models, Established clinical/socioeconomic prognostic indicators	Results demonstrated that, for each cancer site, at least 1 HRQoL domain provided prognostic information that was additive over and above clinical and sociodemographic variables. However, the HRQoL parameters of greatest prognostic value differed across the cancer groups; and the effect size of each HRQoL parameter, indicated by the HR, depended on the tumor site. Physical functioning linked to survival in colorectal cancer (HR: 0.93, 95% CI (0.96-0.99)). Nausea and vomiting significant association in colorectal and ovarian cancer; (HR: 1.06, 95% CI

								(1.01-1.07) and (HR: 1.16, 95% CI (1.07-1.25) respectively.
7	(297)	Robinson et al (2011),	N= 723; Age: NI; M: 0 (0) F: 723 (100)	Gynaecological Denmark	EORTC QLQ-C30	Hypothesised that diagnostic delay could be a indicator of poorer health care system performance, which may affect survival and patient satisfaction. Investigated associations between QoL, patient satisfaction and survival.	Poisson regression modelling and multivariate Cox proportional Hazards models, Demographic/ clinical factors	Association between QoL and survival differed between ovarian and endometrial cancer. In ovarian cancer significant association between increased fatigue and reduced survival (HR: 1.84, 95% CI (1.09-3.10). In endometrial cancer significant association with survival remained after adjustment for physical functioning (HR: 3.30, 95% CI (1.27-8.57), role functioning (HR: 5.40, 95% CI (1.57-18.58), emotional functioning (HR: 3.41, 95% CI (1.33-8.74), nausea (HR: 2.7, 95% CI (1.13-6.45), appetite loss (HR: 3.78, 95% CI (1.71-8.34)
8	(298)	Lehto et al (2018),	N= 104; Age: 66.5 (51-82); M: 104 (100) F: 0 (0)	Prostate Finland	Ways of Coping Questionnaire, Anger Expression Scale, Life Experience Scale, Rotterdam Symptom Checklist,	Investigated the baseline and early predictors of disease-free and overall survival times in prostate cancer patients of all ages and treated with external beam radiotherapy	Multivariate Cox proportional Hazard models, Demographic/ clinical factors	Different QoL measures exhibited either a favorable or an unfavorable impact, i.e., an increased level of pain (HR 0.05; 95% CI 0.01–0.32) predicted longer survival, whereas prostate-area symptoms (HR 1.18; 95% CI 1.03–1.36), increased fatigue (HR 7.08; 95% CI 1.77–28.32),

					EORTC QLQ-C30, LENT-SOMA outcome measure			and reports of no or few physical symptoms (HR 9.90; 95% CI 1.48–66.30) were significant predictors of shorter survival time. However, when the overall quality-of-life index (total scale 1–7) was tested instead of the prostate-area symptom scale, it predicted a longer survival (HR 0.51, 95% CI 0.27–0.95, $p = 0.033$); when both scales were included, the effect of the overall QoL was weaker (HR 0.56; 95% CI 0.27–1.15, $p = 0.113$).
9	(299)	Gupta et al (2015),	N= 917; Age: 63 (40.8-89.3); M: 917 (100) F: 0 (0)	Prostate United States	PS Questionnaire	Investigate whether self-rated health is a potential confounder of the relationship between patient satisfaction with service quality and survival in patients with prostate cancer undergoing treatment.	Multivariate Cox proportional Hazard models, Demographic/ clinical factors	Self-rated health found to be independent predictor of survival in multivariate analysis after controlling for patient satisfaction (HR: 0.30, 95% CI (0.11-0.86). Finding coupled with observation that performance status and self-rated health correlated suggest that self-rated health is potential confounder in relationship between patient satisfaction and survival in prostate cancer.

10	(300)	Jayadeva ppa et al (2009),	N= 318; Age: 57.25 (4.75); M: 318 (100) F: 0 (0)	Prostate United States	SF-36, UCLA Prostate Cancer Index	Analysis of association between race/ethnicity, risk of biochemical recurrence and recovery pattern of patient reported outcomes and cost in younger men with newly diagnosed prostate cancer	Linear mixed effect models, Demographic/ clinical factors	Ethnicity is not a predictor of generic and prostate-specific HRQoL after adjustment for demographic and clinical variables. Low risk of biochemical recurrence was associated with better physical function, vitality, mental health general health, urinary function, bowel function, bowel bother and sexual bother.
11	(301)	Lis et al (2008),	N= 230; Age: 61.8 (40- 87); M: 230 (100) F: 0 (0)	Prostate United States	The Ferrans and Powers Quality of Life Index	Aimed to determine whether patient satisfaction with HRQoL might predict length of survival in patients with prostate cancer undergoing routine oncology treatment	Multivariate Cox proportional Hazard models, Clinical factors	Patient satisfaction with health and physical subscale was significantly associated with survival (RR:0.82, 95% CI (0.67-0.98) Association independent of previous treatment history and Gleason score
12	(302)	Lis et al (2006),	N= 55; Age: 56.2 (33- 74); M: 31 (56.4) F: 24 (43.6)	Pancreatic United States	The Ferrans and Powers Quality of Life Index (QLI)	Determine whether patient satisfaction with QoL predicts length of survival in patients with pancreatic cancer undergoing care in a nonclinical trial setting	Multivariate Cox proportional Hazard models, Disease Stage	Four variables (health and physical subscale, family subscale, global QoL and stage at diagnosis) found to be significant upon univariate analysis. No QoL subscale found to be significant after adjustment for stage at disease although health and physical subscale marginally significant (RR: 0.94, 95% CI (0.89-1.00) (p = 0.053).

13	(303)	Bernhard et al (2010),	N= 295, Age: 63 (26-83); M: 138(46.8) F: 157 (53.2)	Pancreatic Switzerland	Global linear-analogue self-assessment (LASA)	Investigated the prognostic value of QoL relative to CA-19, and the role of CA-19 in estimating palliation in patients with advanced pancreatic cancer receiving chemotherapy within RCT	Multivariate Cox proportional Hazard models and linear mixed effect models	At baseline, less pain and tiredness (i.e. less symptom burden) predicted better survival (HR: 0.65, 95% CI (0.45-0.96)) and (HR: 0.63, 95% CI (0.44-0.92)) respectively. baseline CA 19-9 did not predict QoL or time on study treatment, besides a marginal effect on pain. Neither CA 19-9 nor QoL predicted tumour response to chemotherapy. Survival is influenced by different factors than response to chemotherapy, although response impacts on survival. Thus, CA 19-9 and QoL at baseline provide limited information for estimating palliation by chemotherapy
14	(304)	Gourgou-Bourgade et al (2013),	N= 342; Age: 61 (25-76); M: 211(62.0) F: 131 (38.0)	Pancreatic France	EORTC QLQ-C30	To compare the quality of life (QoL) of patients receiving oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) or gemcitabine as first-line chemotherapy and to assess	Multivariate Cox proportional Hazard models, QoL domains/clinical factors	Performance status, constipation (HR: 1.06, 95% CI (1.01-1.11)) and dyspnoea (HR: 1.06, 95% CI (1.00-1.14)) remained significant after backward and forward selection procedures.

						whether pretreatment QoL predicts survival in patients with metastatic pancreatic cancer.		
15	(305)	Braun et al (2013),	N= 186, Age: 55.1 (24-85); M: 121(65.1) F: 65 (34.9)	Pancreatic United States	EORTC QLQ-C30	Investigate whether pretreatment QoL parameters as well as changes in QoL scores from baseline until 3 months after treatment could predict survival in patients with stage IV pancreatic cancer.	Multivariate Cox proportional Hazard models, Demographic/ clinical factors	Found that every 10-point increase in baseline global QoL score was associated with a 12% decreased risk of death (HR, 0.88; 95% CI, 0.81-0.95; P = 0.001). Improvement in cognitive function at 3 months is an indicator of improved patients' survival after adjusting for other covariates (HR: 0.89, 95% CI (0.77-0.98))
16	(306)	Roychowdhury et al (2003),	N= 364; Age: 63.5; M: 288(79.1) F: 76 (20.9)	Bladder United States	EORTC QLQ-C30	Analysis performed to determine the prognostic significance of HRQoL parameters on time-to-event end points in patients with locally advanced or metastatic bladder cancer who participated in a phase III randomized	Multivariate Cox proportional Hazard models, Demographic/ clinical factors	Identified HRQoL parameters (physical functioning, anorexia, and fatigue) to be significant and independent prognostic factors for time-to-event end points. Physical functioning: (HR:1.56, 95% CI (1.15-2.10)), Anorexia: (HR: 1.84, 95% CI (1.36-2.49)), Fatigue: (HR: 1.46, 95% CI (1.11-1.94))

						study comparing gemcitabine and cisplatin (GC) with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)		
17	(307)	Maisey et al (2002),	N= 501; Age: NI; M: NI F: NI	Colorectal United Kingdom	EORTC QLQ-C30	Examine the prognostic value of baseline QoL measurements in patients with locally advanced and metastatic colorectal cancer treated with systemic chemotherapy within the context of clinical trials	Multivariate Cox proportional Hazard models Clinical/demographic factors	Majority of the QoL domains remained significant independent predictors of overall survival in the final multivariate model: Physical functioning: (HR: 1.35, 95% CI (1.07-1.69)) Role functioning: (HR: 1.34, 95% CI (1.08-1.66)) Social functioning: (HR: 1.43, 95% CI (1.13-1.81)) Emotional functioning: (HR: 1.28, 95% CI (1.04-1.57))
18	(308)	Collette et al (2004),	N= 391; Age: 70.7 (34.3-89.3); M: 391 (100) F: 0 (0)	Prostate Europe	EORTC QLQ-C30	Utilise HRQOL data from three RCTs to assess clinical and biochemical parameters to identify independent prognostic factors for overall survival.	Stratified multivariate Cox proportional Hazard models	Symptom items of appetite loss and insomnia from the EORTC QLQ-C30 were retained as independent prognostic factors of overall survival: Appetite loss: (HR:1.47, 95% CI (1.16-1.86)) Insomnia: (HR:1.45, 95% CI (1.15-1.84))

19	(309)	Stucky et al (2011),	N= 449; Age: 68.8 (11.25); M: 223 (50) F: 226 (50)	Colorectal United States	Symptom Distress Scale, 5-item Quality of Life Index	Evaluate the effect of baseline QOL on subsequent QOL and survival	Intention to treat analysis and stepwise logistic/linear regressions	Baseline outlook [hazard ratio (HR) = 0.58, 95% confidence interval (CI) 0.38–0.88, P = 0.01] and support (HR = 2.85, 95% CI 1.52–5.35, P = 0.001) were significantly associated with overall survival
20	(310)	Chau et al (2004),	N= 1080; Age: 62 (28-84) M: 842 (78) F: 238 (22)	Gastric United Kingdom	EORTC QLQ-C30	Identify baseline patient- or tumor-related prognostic factors and assess whether pretreatment QoL predicts survival in patients with locally advanced or metastatic oesophagus-gastric cancer	Multivariate Cox proportional Hazard models, Clinical/demographic factors	When pretreatment QoL data were tested against the baseline prognostic models, physical functioning (HR: 0.76, 95% CI (0.60-0.97))(P = .003), role functioning (HR: 0.69, 95% CI (0.54-0.88))(P < .001), and global QoL (HR: 0.57, 95% CI (0.45-0.72)) (P < .001) had significant prognostic impact
21	(311)	Coates et al (1997), 47	N= 47; Age: 57.7; M: NI F: NI	Gastric, Colorectal Australia, Germany, Canada	EORTC QLQ-C30	Evaluate the prognostic association of QL scores among patients with advanced malignancies in routine practice	Multivariate Cox proportional Hazard models, Clinical/demographic factors	Single-item QoL scores for overall physical condition, overall quality of life, and the global and social functioning scales remained independently prognostic: Global QoL: (HR: 0.99, 95% CI (0.98-0.99)) Social: (HR: 0.93, 95% CI (0.98-0.99))

HRQoL = Health-related Quality of Life, QoL = Quality of Life, HR = Hazard ratio, CI = Confidence Interval, RR = Risk ratio, OR = Odds Ratio, NI = No information

3.3.1 Quality of Studies

Assessment of each of the included studies, using the relevant JBI critical appraisal checklists per study design, highlighted those studies of particularly good or poor quality. Overall, the quality of each of the studies was deemed reasonable, although a few checklist items pertaining to the quality of the 7 included RCTs were unable to be satisfied. Such checklist items included the concealment or blinding of assigned treatment groups, and subgroup analysis per randomisation group, and none of the included studies were able to provide evidence to satisfy these outlined criteria. Equally, when compared to the case series studies of Lis et al, 2008 (301) and Lis et al, 2006 (302), the case series study by Lehto et al (298) was rated as lower quality. Reasons for this poorer quality grading included a lack of reporting of demographics and clinical information of participants, and a lack of complete inclusion of participants. In contrast, the two case series studies authored by Lis et al satisfied all the quality criteria of the JBI case series critical appraisal checklist. Finally, the quality of each of the included cohort studies was sufficient. The studies by Jayadevappa (300) and Coates (311) were of particularly excellent quality, satisfying all the JBI cohort study critical appraisal checklist items. For the other 9 cohort design studies, some information related to follow-up time, complete follow-up, and addressing incomplete follow-up was either not reported or inadequate.

3.3.2 Data Presentation

Due to a lack of study homogeneity relating specifically to the PROMs utilised in each study, quantitative synthesis was not viable and hence results are presented in a narrative style. A summary of findings for each included study is described in Table 7.

3.3.2.1 Randomised Control Trials

Of the seven RCTs included (295, 303, 304, 306, 308, 309, 310), two were interventions implemented in pancreatic cancer populations (303, 304), two were undertaken in a colorectal cancer setting (295, 309), one in bladder cancer (306), one in gastric cancer (310) and one in prostate cancer (308). Two studies were based on the same RCT (Clinical Outcomes Surgical Therapy (COST) trial NCCTG 93-46-53) but investigated the prognostic significance of measuring baseline patient reported outcomes (PROs) in differing capacities (295, 309). These two studies utilised results from a surgical RCT where the intervention compared open vs laparoscopic techniques in terms of post-operative complications and patient outcomes. Both studies utilised the Symptom Distress Scale and QoL Index collated preoperatively to demonstrate the significant prognostic impact of such quality of life measurements on the overall survival (OS) of colorectal cancer patients. Of note, in the study by Stucky et al, baseline measurements of QoL in terms of patient outlook and availability of support both demonstrated a significant association with overall survival ($HR = 0.58$, 95% CI: 0.38-0.88) and ($HR = 2.85$, 95% CI: 1.52-5.35), respectively. Further analysis undertaken as part of this COST trial

demonstrated that patients with a preoperative QoL deficit were more likely to experience serious post-operative complications, and that use of PRO measures were more sensitive than clinician reported outcomes (CROs) in predicting mortality (295). Of note, longer term combined analysis of patients in both arms of the intervention identified lower patient baseline outlook as associated with decreased overall survival.

Four RCTs comprised secondary analyses of chemotherapy interventions whereby pancreatic, bladder and gastric cancer patients were randomised to receive varying regimens of cytotoxic therapy (303, 304, 306, 310). Noteworthy observations from the study by Bernhard et al included the prognostic significance of pain ($HR = 0.65$, 95% $CI: 0.45-0.96$) and fatigue ($HR = 0.63$, 95% $CI: 0.44-0.92$) as independent indicators for overall survival in pancreatic cancer, although these measures were found to be less prognostic than observed levels of the carbohydrate antigen 19-9 (CA-19) (303). In addition, this study surmised that QoL did not predict tumour response to chemotherapy.

Furthermore, the study by Gourgou-Bourgade et al revealed physical functioning, constipation, and dyspnoea as independent and significant prognostic factors for OS in pancreatic cancer patients with metastatic disease receiving either FOLFIRINOX or Gemcitabine chemotherapy (304). This study involved administration of the EORTC QLQ-C30 questionnaire to 342 patients with metastatic disease. Overall, severely impaired physical functioning imparted the strongest negative effect on OS. The final hazard ratios and 95% confidence intervals for each significant QoL domain are reported following multivariate analysis: physical functioning ($HR = 0.88$, 95% $CI: 0.81-0.96$), constipation ($HR = 1.06$, 95% $CI: 1.01-1.12$) and dyspnoea ($HR = 1.10$, 95% $CI: 1.02-1.18$).

In the context of the bladder cancer RCT, Roychowdhury et al also utilised the EORTC QLQ-C30 questionnaire to demonstrate physical functioning as a significant and independent prognosticator for various time to event endpoints including overall survival, time to progressive disease, and time to treatment failure (306). Time to progressive disease was defined in this study as the date of random assignment of chemotherapy (gemcitabine and cisplatin (GC) vs methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)) until death or disease progression. This RCT also identified a potential prognostic role for minimal fatigue and absence of anorexia in both treatment arms. For example, multivariate analysis for overall survival observed a hazard ratio of 1.84 (95% $CI: 1.36-2.49$) for anorexia and a hazard ratio of 1.46 (95% $CI: 1.11-1.94$) for fatigue. Interestingly, in univariate analysis, higher role functioning was identified as a positive prognostic factor for OS but, paradoxically, in the multivariate model longer OS was associated with lower role functioning.

As part of the multi-centre pooled analysis by Chau et al, patients with locally advanced or metastatic esophago-gastric cancer completed the EORTC QLQ-C30 cancer generic questionnaire (310). This pooled multivariate analysis identified a statistically significant association of pre-treatment QoL data with overall survival. Specifically, physical functioning ($HR = 0.76$, 95% CI: 0.60-0.97), role functioning ($HR = 0.69$, 95% CI: 0.54-0.88) and global QoL ($HR = 0.57$, CI: 0.45-0.72) domains of the cancer generic EORTC module exhibited significant prognostic impact in this population.

In contrast to the other reported RCTs, a European hormonal therapy/radiotherapy intervention in prostate cancer identified that HRQoL factors, as measured by the EORTC QLQ-C30 instrument, did not accurately predict overall survival once clinical and biochemical factors were accounted for (308). Despite baseline global health status being associated with overall survival in other tumour types, this relationship was not demonstrated in this study. Only the EORTC QLQ-C30 symptom items of appetite loss and insomnia remained as independent prognostic factors of overall survival in multivariate models, in addition to haemoglobin level, number of bone metastases on initial bone scan, and initial WHO performance status. The results of this study indicate that these factors may prove useful in predicting average overall survival at patient group level alone.

3.3.2.2 Cohort Studies

Full details of the 11 included cohort studies are presented in Table 7. One study was conducted in the context of aggregated RCT data (296) and ten were original cohorts (291, 292, 293, 294, 297, 299, 300, 305, 307, 311). The tumour breakdown of these patient cohorts was as follows: five analyses included urological cancer patients (291, 292, 296, 299, 300), four colorectal (291, 296, 307, 311), three gynaecological (291, 296, 297), three pancreatic (293, 294, 305) and one gastric cancer cohort (311).

An analysis by Jayadevappa et al of 318 younger prostate cancer patients (≤ 65 years of age at diagnosis) identified that low risk biochemical recurrence is mostly indicative of better generic and prostate specific HRQoL (300). Similarly, an American analysis of 917 prostate cancer patients demonstrated that patient self-rated health is a potential confounder in the relationship between patient satisfaction and survival; thus suggesting that future studies investigating patient satisfaction should include collection of self-rated health modules ($HR = 0.30$, 95% CI: 0.11-0.86) (299). In renal cancer, a study by Graham et al observed that baseline use of the Edmonton Symptom Assessment System provided a modest degree of prognostic information about survival, independently of other widely used prognostic models (292). In multivariate analysis, higher baseline symptom burden was associated with inferior overall survival ($HR = 1.21$, 95% CI: 1.01-1.44) for each ten-unit increase in

the Edmonton Symptom Assessment Symptom total score, and when controlling for Memorial Sloan Kettering Cancer Centre defined risk groups for metastatic disease. These results were consistent with previously reported data examining the prognostic function of the FACT-KSI instrument.

In pancreatic cancer patient cohorts, analyses further suggested a role for the EORTC QLQ-C30 instrument to provide prognostic information for survival (305). As reported above, baseline global health was an independent prognosticator and, interestingly, the study found that the probability of survival increased significantly if cognitive function improved within three months of treatment (305). Specifically, this study identified that every 10-point increase in baseline global QoL score was associated with a 12% decreased risk of death ($HR = 0.88$, 95% CI: 0.81-0.95). Of note, an analysis of 66 Norwegian pancreatic cancer patients also demonstrated that cognitive function, as measured by the Edmonton Symptom Assessment Scale, was an independent prognostic factor (293). In this analysis by Baekelandt et al, patients were divided into two groups comprising high vs low cognitive function. When compared to patients with higher cognitive functioning, the hazard of death was significantly higher for patients with low cognitive function ($HR = 3.5$, 95% CI: 1.7-7.3).

In the context of colorectal cancer, a large UK study of 501 patients identified that patients with high baseline global QoL have a 1-year survival that is almost double that of patients with a score below median value (307). Multivariate analysis also demonstrated that symptom and functioning measures, as recorded using the EORTC QLQ-C30, appeared to be a stronger predictor of overall survival compared to clinician measured performance status. Hazard ratios and accompanying confidence intervals for such multivariate analysis are presented: physical functioning ($HR = 1.35$, 95% CI: 1.07-1.69), role functioning ($HR = 1.34$, 95% CI: 1.08-1.66), social functioning ($HR = 1.43$, 95% CI: 1.13-1.81), and emotional functioning ($HR = 1.28$, 95% CI: 1.04- 1.57). A smaller analysis of 47 patients with advanced gastric or colorectal cancers identified that overall physical condition and global QoL was an independent prognosticator of overall survival (311). Indeed, further preliminary analyses demonstrated an association between psychological response to cancer and survival. In addition, social functioning exhibited significant prognostic functionality ($HR = 0.93$, 95% CI: 0.98-0.99) although this association was borderline significant.

A Danish analysis of a gynaecological patient cohort investigated patient QoL and satisfaction as an alternate avenue for exploring the consequences of diagnostic delay (297). This study identified that, in ovarian cancer patients specifically, fatigue was associated with reduced overall survival ($HR = 1.84$, 95% CI: 1.09-3.10). In a subset of the cohort with endometrial cancer, several QoL domains including overall QoL, physical, emotional and role functioning, nausea and vomiting, pain, dyspnoea, and appetite loss were independently associated with survival (297). Such associations

remained significant after adjustment, although reported confidence intervals are wide: physical functioning ($HR = 3.30$, 95% CI: 1.27-8.57), role functioning ($HR = 5.40$, 95% CI: 1.57-18.58), emotional functioning ($HR = 3.41$, 95% CI: 1.33-8.74), nausea ($HR = 2.7$, 95% CI: 1.13-6.45), and appetite loss ($HR = 3.78$, 95% CI: 1.71-8.34).

3.3.2.4 Case Series

Three studies recruited prostate and pancreatic cancer patients consecutively (298, 301, 302). In the context of radiotherapy, overall survival, and disease-free survival in prostate cancer patients with localised disease were predicted by socioeconomic status, psychological factors, and patient self-reported QoL (298). In this study, different QoL domains demonstrated favourable or unfavourable impact; patients with reports of few or no physical complaints predicted shorter survival whereas reported pain was prognostic for longer overall survival.

A case series of 55 pancreatic cancer patients identified a borderline significant association between baseline health and physical measures, and survival after adjustment for disease stage at diagnosis ($RR = 0.94$, 95% CI: 0.89-1.00) (302). Indeed, this study also suggested that patient satisfaction with QoL provides useful prognostic information. Finally, a study of 230 consecutive prostate cancer patients determined that patient satisfaction with their HRQoL was significantly associated with overall survival. This association remained significant independently of previous treatment and Gleason score ($RR = 0.82$, 95% CI: 0.67-0.98).

3.4 Discussion

This systematic review identified several domains of QoL as potential prognosticators for oncological outcomes in tumours of the pelvic abdominal cavity. Specifically, global QoL and fatigue, as well as physical, emotional, social, and role functioning, consistently emerged as independent prognostic factors for overall and disease-free survival across the included tumour types (291, 295, 297, 302, 305, 306, 307, 310, 311). Other domains related to pain, constipation, dyspnoea, anorexia, appetite loss, nausea, and cognitive function also appeared to have a potential prognostic function, independently of the clinicopathological features of disease (293, 295, 303, 304, 305, 306). Finally, one study identified a prognostic association between baseline measurements of patient outlook and support, and overall survival (309).

The observed potential association between physical functioning and OS has been demonstrated in multiple studies of various tumour types outside of those investigated in this review (312, 313). One large review by Gotay et al reported that physical functioning was a prognostic indicator in 11 of 39 studies investigated (314). A further study by Mol et al concluded that physical functioning, as

assessed by patient self-report methods, had more prognostic value for predicting overall survival than clinician-assessed WHO performance status (315).

Regarding the potential association between emotional functioning and OS, a large longitudinal study of head and neck cancer patients identified a relationship between symptoms of depression and shorter survival time (316). These results were also mirrored in further community based and disease specific studies investigating the association between depression and mortality (317).

The relationship between global QoL and survival has also been investigated in alternate tumour types, such as in a study of non-small cell lung cancer patients (318). This study surmised that every 10-point increase (or betterment of) global quality of life was associated with a 9% increase in survival.

Considering the observed prognostic potential of self-report fatigue, a large study of 1588 primary breast cancer patients also demonstrated a significant association between low levels of fatigue and increased recurrence-free survival (319).

Role functioning, or limitations related to performance in terms of employment, caring, being a spouse or partner, and being involved in community activities, also emerged as a prognostic factor. Similarly, an alternate study of patients with cirrhosis noted a significant association between a deficit in role functioning and reduced overall survival (320). Equally, social stressors such as a patient's perceived levels of social support were found to be associated with mortality in cancer patients included in the University of North Carolina Cancer Survivorship Cohort (321). In this cohort, individuals who reported a higher level of satisfaction with their social support had a lower mortality risk than those individuals reporting lower levels of satisfaction. This study hypothesised that inflammatory processes related to low levels of CRP, IL-6, and TNF- α may underpin this observed association.

Despite compelling published evidence observing the prognostic role of baseline QoL measurements, the causal relationship between QoL and overall survival remains enigmatic. It has previously been suggested that collection of self-reported QoL measurements may be a more accurate indicator of underlying severity of disease compared to other crude measurements such as tumour burden (322). Indeed, previously published studies have observed the superior nature of QoL in assessing prognosis compared to tumour burden; Earlam et al successfully utilised physical QoL score to predict the overall survival of colorectal patients with liver metastases receiving supportive care alone and identified that the extent of metastasis did not influence survival (323). In addition, historical studies in lung cancer (324, 325) identified QoL as an independent prognostic

factor for survival but failed to identify a significant relationship between survival and number of metastatic sites or disease extent. It is hypothesised that tumour markers which accurately reflect tumour aggression may also impact patient QoL more significantly than tumour burden (307).

Equally, various studies have hypothesised that QoL may directly impact tumour behaviour and subsequent patient survival, although such evidence is limited and controversial. Multiple studies (326, 327, 328) suggested that improvements in QoL or patient mental and emotional wellbeing may influence survival but were limited by small patient numbers. In comparison, a larger study of more than 1000 head and neck cancer patients found no link between emotional wellbeing and survival in this patient group (329).

Gotay et al also presented various potential explanations for the observed association between health-related QoL and overall survival in cancer outcome studies (314). Firstly, the authors noted the variety in content of QoL measures and hypothesised that QoL measures may provide more sensitive information compared to traditional performance status and toxicity measures. Secondly, the authors hypothesised that QoL data collated at baseline and prior to disease progression may provide earlier insight than established clinical prognostic factors. Alternatively, they suggested that QoL data are markers of a patient's behaviour as data relates to diagnosis, treatment, and subsequent outcomes of the disease. Finally, Gotay et al indicated that QoL data are individual markers of characteristics which may affect the disease process and outcomes in cancer patients.

A further possible explanation for the association between self-rated health measures and overall survival may lie in the context of the body-mind relationship. One published study suggested that self-reported health is a unique indicator of human health status (330). The origins of this theory incorporate a process whereby information from an individual's body and mind is processed, reviewed, and summarised by the individual themselves to predict the most absolute biological events, such as death.

Finally, this relationship may be explained by quality-of-life markers being indicators of the socio-economic status of the patient. Robust evidence exists to suggest that cancer patient socio-economic status predicts survival – for example a cancer patient of a higher social class is expected to have better quality of life and consequently may survive longer (331). Overall, the potential underlying mechanistic action of QoL monitoring and impact on patient survival requires more investigation.

Despite the evident prognostic potential of PROMs, this review of the literature suggests that most PROMs are collected in the context of scientific research rather than routinely in the cancer clinical

setting. Although it is well-established that patient perspective is an integral component of high quality and patient-centred care (332), financial burden and logistical issues prevent many healthcare systems from adopting PROM collection (25), and there exists a lack of uniform approach for their implementation in cancer specifically (26). The PRISMA study, which primarily surveyed clinicians from Europe or Africa, highlighted physician time constraints and patient factors as key barriers to PROM implementation within the palliative care setting (333). Additionally, a lack of training and guidance for clinicians were identified in this study as factors preventing wide-spread roll-out, and Gibbons et al identified difficulties relating to budget and available software tools as further barriers to successful implementation (334).

There also exists a lack of validated tumour specific outcome measurement tools in cancer. Within this review, most studies utilised baseline measurements of the cancer generic EORTC QLQ-C30 instrument. Although a standard tool for measuring HRQoL, the instrument lacks sensitivity to subtle disease specific changes (335). Impetus therefore lies with the development and validation of disease specific instruments which can detect and quantify subtle changes in disease and accurately inform treating clinicians and the patients (336).

It is also of note that this review was undertaken during the COVID-19 pandemic when fears around the longer-term burden of SARS-CoV-2 on cancer care were emerging. During the outbreak, outpatient cancer care underwent a perhaps perpetual paradigm shift towards remote telemedicine, which further highlighted the necessity of routine collection of PROMs to support patients and allow shared clinical decision-making.

Overall, the results of this study indicate a value for the complementary assessment of health-related quality of life as an addition to standard of care clinical investigations. As observed in this review, symptom monitoring, with a particular focus on functioning, global QoL and fatigue, appear to be associated with survival. Therefore, the addition of HRQoL scales to routine care practices will provide the most comprehensive picture of a patients' health and allow tailoring of personalised treatment pathways to maximise survival.

3.4.1 Limitations

Many of the analyses included large patient numbers and therefore the findings of this review can be assumed robust. There did, however, exist heterogeneity in the study design and methodology of the included studies which ultimately prohibited a collective meta-analysis of the reported data. Ten of the included studies were conducted using data collated in the United States where private health care is prevalent, and therefore the results of these studies may not be generalisable across other populations. Equally, most of the included analyses (13/21) covered pancreatic and prostate tumour

types alone. Although the shorter and longer survival times associated with these cancers provide a comprehensive overview of quality of life across the full cancer journey, these cancers are analogous with a specific age range and the male sex. Therefore, the prognostic potential of QoL measures is less well understood in other tumour types of the pelvic abdominal cavity and may differ by sex and age. Further investigation into the prognostic potential of PROMs is warranted in such tumour types with limited existing evidence.

3.5 Conclusions

Overall, the findings of this review suggest a complementary role for the routine collection of PROMs in tumours of the pelvic abdominal cavity to improve patient quality of life and outcomes and facilitate personalised care. Specifically, baseline measurements of global QoL, fatigue, and functioning consistently emerged as independent prognosticators indicative of survival across these tumour types.

Chapter IV:

Selection of PROMs

This chapter is formed of three successive projects which were undertaken to select PROM tools for collection at Guy's Cancer Centre. The first project involves the identification of relevant PROMs; the second project includes psychometric appraisal of the identified instruments; and the third project comprises a local consensus process to select PROM tools.



Chapter IV:

Selection of
PROMs

Chapter I:

Summary of
Thesis

Chapter II:

Background
and aims

Chapter III:

Prognostic
function of
PROMs

Chapter V:

Feasibility study
of PROM
collection

Chapter VI:

Mixed methods
evaluation

Chapter VII:

Conclusions and
future directions

Chapter IV: Selection of PROMs

4.1 Background

Chapter III outlined a rationale for the collection of patient-reported outcome measures (PROMs) routinely in clinical practice. In summary, it is well established that PROMs can be employed to facilitate shared decision making, incorporate patient perspective of experience, and enhance patient-centred care. In addition, Chapter III presented data to further support routine clinical PROM collection by reporting a potential prognostic role for PROMs collected at baseline and follow-up timepoints. In this systematic review, baseline measurements of self-report global QoL, fatigue and functioning domains consistently emerged as independent predictors of oncological outcomes, suggesting that complementary collection of PROMs can be utilised to predict outcomes in the routine setting.

Further to the observed individual patient-level benefits, aggregated population data can be used at local and national levels to direct service evaluation and quality improvement, and to inform policymakers and guideline development. Moreover, PROMs can be used in benchmarking projects which are developed to allow comparisons across clinical groups. Clearly, there exists a real and significant need for the collection of clinically relevant PROM tools in routine care settings, not least for the purposes outlined above.

Having established the benefits of routine PROM collection, the next project aimed to objectively select the most appropriate tools to use in the standard clinical setting. This is the focus of this chapter of the thesis.

4.2 Rationale

Despite the presented compelling evidence to favour routine clinical PROM collection, a key emerging barrier to successful implementation is selection of the most appropriate tool(s) to fulfil the purpose of measurement in the population of interest.

In recent decades, the availability of both generic and disease-specific PROM instruments applicable to cancer populations has increased exponentially, and more novel tools are being developed each year. The increasing availability of PROM instruments presents a decision-making challenge for healthcare systems aspiring to commence routine clinical collection. When selecting a PRO measure, various factors should be considered: validity (does the PROM measure what it is intended to measure?), reliability (are the conditions the same each time?) and sensitivity (does the instrument detect real differences?). Equally, information related to patient and administrator burden, recall

period, availability/licensing of the instrument, and scoring should be incorporated in the deliberation process.

Furthermore, the PROM selection process should fulfil each of the patient-level, local, and national use purposes as outlined above. Standardisation, or local and/or national alignment of PROM measures should be integrated into the selection process, to enable benchmarking across clinical groups.

Overall, considering the necessity of ensuring multi-level applicability and standardisation, the selection of PROMs forms a critical step in certifying the successful implementation of routine clinical collection. Despite this, there currently exists a lack of accepted standards on which PROMs should be applied in which setting, which, when coupled with a lack of data on the quality and validity of each instrument, has resulted in heterogeneity in the use and reporting of PROMs both in the research and clinical setting.

The following Chapter of this thesis therefore sought to overcome the aforementioned barrier of PROM selection to facilitate implementation in the routine clinical setting. The Chapter is formed of three successive projects, each linked, and presented in stepwise fashion:

- Overall, Project 1 was conducted to identify any relevant PROM instruments for application in cancers of the pelvic abdominal cavity.
- Project 2 involved the appraisal of the quality, validity, and reliability of the gynaecological PROM instruments identified in Project 1 and was undertaken concurrently with the identical work of the IMI PIONEER Consortium (PIONEER) for prostate cancer. The work of PIONEER is external to this thesis; however, a brief background is provided below to provide context to the reader.
- Project 3 subsequently incorporated a consensus process to select PROMs for implementation in the prostate and gynaecological oncology setting at Guy's Cancer Centre, using data from Project 2 of this thesis as well as the results of the PIONEER studies.

As mentioned above, the IMI PIONEER Consortium undertook concurrent work to identify relevant PROM tools applicable to prostate cancer populations, and independently appraised the quality, validity, and reliability of these tools externally to this thesis. I was an active collaborator in this parallel work and my contributions are recognised in publication co-authorship. A brief overview of PIONEER is included below (section 4.2.1). Additionally, Table 8 is included to illustrate the content of this chapter including detailing of whether the work was undertaken within this thesis or externally, as part of PIONEER.

Table 8: Table illustrating the content of Chapter IV of this thesis, including which tumour types were included within each Project. Green indicates that the project was undertaken as part of this PhD project, and yellow signifies work which was undertaken externally by the IMI PIONEER Consortium.

	Project 1 - Identification of PROMs	Project 2 - Appraisal of PROM quality, validity & reliability	Project 3 - Local consensus process
Ovarian	<i>Thesis</i>	<i>Thesis</i>	<i>Thesis</i>
Cervical	<i>Thesis</i>	<i>Thesis</i>	<i>Thesis</i>
Endometrial	<i>Thesis</i>	<i>Thesis</i>	<i>Thesis</i>
Vaginal	<i>Thesis</i>	<i>Thesis</i>	<i>Thesis</i>
Vulval	<i>Thesis</i>	<i>Thesis</i>	<i>Thesis</i>
Prostate	IMI PIONEER	IMI PIONEER	<i>Thesis</i>
Renal	<i>Thesis</i>	x	x
Bladder	<i>Thesis</i>	x	x
Pancreatic	<i>Thesis</i>	x	x
Hepatic	<i>Thesis</i>	x	x
Gastric	<i>Thesis</i>	x	x
Colorectal	<i>Thesis</i>	x	x

4.2.1 IMI Prostate PIONEER Consortium

Briefly, the IMI Prostate PIONEER Consortium, or PIONEER, is a project which received funding as part of the IMI's Big Data for Better Outcomes (BD4BO) programme. The BD4BO programme aims to improve health outcomes and healthcare systems across Europe by harnessing the potential of Big Data. PIONEER seeks specifically to transform prostate cancer care across Europe with a focus on outcomes, health system efficiency, and the quality and availability of health and social care. Currently the PIONEER Consortium involves 32 partners located across a European Network of Excellence for Big Data in Prostate Cancer spanning 9 countries. The overall goal of the programme centres around ensuring optimal care for all European prostate cancer patients. There are 8 defined work packages, each including distinct aims and objectives; work package 2 for example involves the development of standardised definitions of prostate cancer outcomes, and diagnostic and prognostic factors previously prioritised across each stage of disease. The individual objectives of this work package include identification of core outcome sets and diagnostic and prognostic factors for localised, locally advanced, and advanced-metastatic prostate cancer, in the context of the patient's treatment journey, and including quality of life, patient-reported outcomes, and economic endpoints. The second objective of this work package involves assessment of priority for each identified outcome, diagnostic and prognostic factor, and ultimately aims to recommend a valid and feasible outcome measurement instrument. Such outlined objectives closely align with the objectives of this thesis chapter, and the work of Project 1 and Project 2 occurred concurrently with

the work of the PIONEER Consortium. The results of these assessments are published in the European Urology Oncology (localised prostate cancer) and Cancers (metastatic prostate cancer) journals, and relevant recognition for my contribution in these projects is provided in the form of co-authorship (337, 338). A brief summary presenting the key results of these papers is included between Project 2 and 3 (section 4.5) to provide further context for the reader. Presented results were taken forward to inform the consensus process (Project 3) for the selection of PROMs for use in the prostate clinical oncology setting at Guy's Cancer, specifically.

4.2.2 Project 1 - Identification of PROM measures

Firstly, a systematic search of the literature was undertaken to identify any PROM instruments developed for, or previously applied in, tumours of the pelvic abdominal cavity. This search is referred to as Project 1. Such search was undertaken to reflect the inclusion criteria utilised in Chapter III and includes all tumours of the pelvic abdominal cavity, except for prostate cancer which is omitted. For the purposes of Project 1, prostate cancer was excluded from the search criteria, so as to not duplicate the concurrent work of the IMI Prostate PIONEER Consortium (see above).

4.2.3 Project 2 - Appraisal of gynaecological cancer PROM quality and validity

Following the identification of relevant and applicable PROM instruments across each pelvic abdominal tumour type (except prostate), the PROM measures identified as applicable or relevant for use in gynaecological cancer patient populations specifically were taken forward and assessed using the CONsensus-based Standards for the selection of health Measurement INSTRuments (COSMIN) guidelines. These guidelines were employed to (1) evaluate the quality of the identified PROMs through assessment of defined measurement properties; and (2) report the methodological quality of studies to determine the trustworthiness of the results regarding PROM quality and validity. This study is denoted as Project 2. The IMI PIONEER Consortium undertook concurrent appraisal of prostate PROM measures according to the COSMIN guidelines in parallel with the work of this thesis.

4.2.4 Project 3 - Local consensus process

Finally, two internal consensus processes were undertaken independently to select the most appropriate PROM tool(s) for collection in the prostate and gynaecological cancer clinical settings of Guy's Cancer Centre. These internal consensus processes are referred to as Project 3 within this Chapter, and utilise data harnessed from Project 1 and 2.

4.3 Project 1 - Identification of PROM Measures

4.3.1 Rationale

The full aims of Project 1 are detailed above, however, briefly, the aim of Project 1 was to identify PROM tools developed for use in, or previously applied in, the population(s) of interest. For the purposes of this systematic search, all tumours of the pelvic abdominal cavity were selected, except for prostate cancer which was omitted owing to the parallel work of the PIONEER Consortium. PROM instruments identified across each overarching tumour grouping (gynaecological, urological, colorectal, hepatic, pancreatic, and gastric) are reported for information. The results of the search do, however, include a focus on the gynaecological cancer studies specifically, owing to the overarching aims of this thesis and the work included in the subsequent Projects of this Chapter.

Results specific to gynaecological cancers have been accepted for publication and are in press, along with findings from Project 2, in the *Future Oncology* journal (Moss, Guerrero-Urbano, *et al.*, 2022).

4.3.2 Methods

4.3.2.1 Search Strategy and Inclusion Criteria

Both the search aim and strategy, and inclusion and exclusion criteria were developed *a priori* of literature searching which commenced in February 2020. Studies utilising PROM instruments in the population(s) of interest were identified by conducting searches of Medline (Pubmed) and Ovid Gateway (Embase and Ovid). Searching was undertaken using a time period limiter of 1st January 2008 – 28th February 2020 and subsequent returned results were further limited to studies involving humans alone. The comprehensive search strategy is included below for reference:

Kidney cancer or renal cancer* or kidney neoplasm* or renal neoplasm**
Bladder cancer or bladder neoplasm* or bladder tumor* or bladder tumour* or urinary bladder cancer* or urinary bladder neoplasm* or malignant tumor of urinary bladder**
Cervix cancer or uterine cervical cancer* or cervical neoplasm* or cervix neoplasm* or uterine cervical neoplasm**
Vagina cancer or vagina* neoplasm**
Ovary cancer or ovarian cancer* or ovary neoplasm* or ovarian neoplasm**
Vulva cancer* or vulva* neoplasm**
Endometr cancer or endometr* neoplasm* or uterine neoplasm**
*Fallopian tube cancer or fallopian tube neoplasm**
Hepatic cancer or liver cancer or hepatocellular cancer or hepatic neoplasm or hepatic neoplasm* or hepatocellular neoplasm**
Gastric cancer or stomach cancer* or gastric neoplasm* or stomach neoplasm**
Colon cancer* or colon* neoplasm**
Pancreas cancer or pancreatic cancer* or pancreas neoplasm* or pancreatic neoplasm**
Rect cancer* or rectal tumour or rectal tumor or rect* neoplasm**
Anal cancer or anal neoplasm* or anus cancer* or anus neoplasm**
Patient reported outcome or patient reported outcome measurements or PROM or patient satisfaction or PREM or PRO or outcome measure or outcome assessment or outcomes research or outcome study*
Hrqol or health related quality of life or health-related quality of life or life quality or quality of life or QoL
(Survey or survey) and questionnaire or respond or survey method* or assessment or report or relate* or apprais**
limit to (humans and yr="2008 -Current")

After searching, the list of returned articles was filtered to include only articles published in the English language.

The following inclusion criteria was utilised: a randomised control trial, observational study, systematic review, or meta-analysis, editorial, or an original article, written in the English language, and involving the development or application of at least one PROM instrument in the population(s) of interest. To clarify, the tumour types of interest in this systematic search included urological (renal and bladder), gynaecological (cervical, ovarian, endometrial, vulval, and vaginal), colorectal (colon, rectal and anal), gastric, hepatic, and pancreatic cancers. Commentaries, author's replies, and supplements were excluded as well as studies on prostate cancer populations alone. Studies that

included patients with cancers other than pelvic abdominal tumours, or prostate cancer patients, were included on the condition that the PROM instruments relevant to each pelvic abdominal cancer type could be identified independently of other disease specific tools.

All duplicates were removed, and articles were reviewed by title, abstract and full text by the first author (CM). A second author (MVH) subsequently reproduced the results of the search strategy. PROM tools relevant to each included tumour type were identified within each study and listed by cancer type. Accompanying study characteristics related to study type, study setting, treatment modality, patient numbers, and whether PROMs were collected as a primary or secondary outcome were further extracted and reported. Management of the screening process and collation of the review data occurred using Microsoft Excel.

4.3.3 Results

Overall, the search strategy identified 5420 articles. After duplicates were removed, 5392 unique studies remained and underwent title screening according to the outlined inclusion criteria. Following title screening, a further 699 records underwent abstract review before 479 articles were reviewed based on the full text. Information related to PROM instrument(s) used, cancer type(s) included within the study, the study design, the number of study participants, collective disease stage of the study population, and whether PROMs were collected as a primary or secondary outcome was collated for each of the 479 articles. Note, various of the articles included multiple cancer types, hence the summation of the number of included studies per tumour type exceeds 479.

4.3.3.1 Gynaecological Cancers

Of the 479 included full text articles, 137 involved patients with a gynaecological cancer. Overall, the most utilised PROM across the gynaecological cancer cohort was the cancer generic European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 which was employed in 59 of the 137 studies. The EORTC cervical cancer (EORTC QLQ-CX24) and ovarian cancer (EORTC-OV28) supplementary modules were the next most utilised instruments, and were applied in 27 and 19 studies, respectively. A number of generic PROM instruments including the SF-36, Hospital Anxiety and Depression Scale (HADS), EQ-5D, and Brief Pain Inventory (BPI) were used in multiple studies; the SF-36 was applied in 16 studies, HADS in 12, EQ-5D in nine studies, and Brief Pain Inventory used in two. In total, 55 differing PROM tools were identified as utilised in 137 gynaecological oncology studies with 35 generic and/or disease-specific PROM tools employed in one study each. A full list of the 55 PROMs developed for, or applied in, gynaecological cancer patient populations is included in Table 9.

Table 9: List of all PROM instruments identified as developed for or applied within a gynaecological cancer setting.

PROM	Gynaecology (n=137)
EORTC QLQ-C30	59
EORTC QLQ-CX24	27
EORTC QLQ-OV28	19
FACT-O	17
SF-36	16
FACT-G	13
Hospital Anxiety and Depression Scale	12
FACT-CX	10
EQ-5D	9
Female Sexual Function Index	8
EORTC QLQ-EN24	4
FACIT-Spiritual	4
SF-12	4
WOMAN-PRO	3
Impact of Event Scale	2
Measure of Ovarian Symptoms and Treatment	2
FACT-GOG/Ntx	2
Brief Pain Inventory	2
Life Orientation Test	2
State Trait Anxiety Scale	2
Assessment of Survivor Concerns, Brief Illness Perception, Self Regulation Questionnaire, Changes in Sexual Function Questionnaire, COPE, Distress Thermometer, Leiden Questionnaire, Pelvic Floor Assessment Questionnaire, Subscales for Bowel and Bladder Symptoms, Impact of Cancer Questionnaire, Incontinence Impact Questionnaire, Female Sexual Distress Scale, FACIT-F, Center for Epidemiological Studies Depression Scale, Profile of Moods States, Symptom Distress Scale, FACIT-Ovarian, Neurotoxicity Scale, FACT-EN, FACT-Neutropenia, FACT-T, Insomnia Severity Index, WHO QoL Brief Scale, Ronsenberg Self-esteem Scale, Satisfaction with Decision Scale, Sexual Quality of Life Questionnaire, Multidimensional Scale of Perceived Social Support , Locus of control scale, Edmonton Symptom Assessment Scale, Templers Death Anxiety Scale, Herth Hope Index, Psychological General Well-being Index , MAYO 10-point linear scale, Australian Pelvic Floor Questionnaire, 12-item General Health Questionnaire	1

Further details regarding the study characteristics of the 137 gynaecological cancer specific studies are included in Appendix III. Of note, 29 of the 137 studies were of randomised control trial design and patient numbers ranged from 8-17,000. In total, 33 included studies involved survivors of a gynaecological cancer and 21 studies were conducted in gynaecological cancer patients with locally advanced or advanced disease. Chemotherapy was the most common treatment modality of the

included studies, with 35 of the 137 studies including gynaecological cancer patients undergoing systemic treatment. Overall, 103 of the studies investigated PROMs as the primary study outcome.

4.3.3.2 Other pelvic-abdominal cancer types

After gynaecological cancers, colorectal cancer had the second highest number of included studies, with 114 full text studies appraised. Similarly with gynaecological cancers, the EORTC QLQ-C30 cancer generic questionnaire was the most frequently administered PROM. Following the EORTC QLQ-C30, the now superseded EORTC QLQ-CR38 colorectal cancer module was the second most commonly used PROM, in 60 studies. The EORTC QLQ-CR38 colorectal module became outdated in 2007 when it was replaced by the updated EORTC QLQ-CR29. This colorectal submodule was employed in 18 studies. The Functional Assessment of Cancer Therapy – Colorectal (FACT-C) tool was also utilised in a significant number of studies, applied in 15 out of 114 studies overall. Details of the full list of PROMs identified as applied in a colorectal setting are included in Table 10.

Table 10: List of all PROMs identified as developed for or applied within a colorectal cancer setting

PROM	Studies used (of 114)
EORTC QLQ-C30	72
EORTC QLQ-CR38	60
EORTC QLQ-CR29	18
FACT-C	15
SF-36	15
EQ-5D	6
Fecal Incontinence Quality of Life Scale	5
Hospital Anxiety and Depression Scale	5
Faecal Incontinence Severity Index	4
FACT-G	4
International Index of Erectile Function	4
International Prostate Symptom Score	4
Memorial Sloane-Kettering Cancer Center Bowel Function Instrument	3
Wexner Incontinence Score	3
Duke-UNC Functional Social Support Questionnaire	3
Low Anterior Resection Syndrome Score	3
Female Sexual Function Index	3
State Trait Anxiety Inventory	2
Medicare Health Outcomes Survey	2
Quality of Life in Rectal Cancer Patients (QoLiRECT)	2
City of Hope Quality of Life-Ostomy	2
The Social Difficulties Inventory	2
Body Image Scale	2
Scale of Chemotherapy-Induced Long-Term Neurotoxicity; Impacts of Events Scale; St Mark's Incontinence Score; Faecal Incontinence and Constipation Questionnaire; Illness Cognition Questionnaire; Inflammatory Bowel Disease Patient Concerns; Brief Pain Inventory; International Consultation on Incontinence Questionnaire; American Urological Association Symptom Index; Brief Sexual Function Inventory; Colorectal Functional Outcome Questionnaire; Gastrointestinal Quality of Life Index; Self-Rating Depression Scale; Medical Coping Modes Questionnaire; Social Support Rating Scale; The Quality of Life Scale; Coping Inventory for Stressful Situations; Life Events Scale; Cleveland Clinic Incontinence Score; SF-12; QoR-40; Korean Mini-Mental State Examination; Everyday Cognition; Quality of Working Life Questionnaire for Cancer Survivors; Barthel Index; Social Impact Scale; Sexual Quality of Life Questionnaire; Sexual Function Vaginal Changes Questionnaire; The Female Sexual Distress Scale; The Rosenberg Self-Esteem Scale; Edmonton Symptom Assessment Scale	1

The full list of PROMs identified within the urological tumour setting are included in Table 11,

omitting PROMs which may be relevant or applicable in prostate cancer populations. Overall, 82 full text articles including renal and/or bladder cancer patients were screened to identify PROM instruments employed in the respective studies. Interestingly, despite the EORTC QLQ-C30 questionnaire again being the most utilised (in 27/82 studies), the second most applied PROM was the generic SF-36 tool which measures 8 domains related to general health. The Functional Assessment of Cancer Therapy – Bladder (FACT-BL) and Bladder Cancer Index tools were identified as utilised in 10 and 9 studies, respectively. The FACT-BL PROM assesses domains related to physical, social, emotional, and functional well-being, and addresses bladder cancer specific domains related to urinary, bowel and sexual functioning. Similarly, the Bladder Cancer Index assesses urinary function, bowel habits, and sexual functioning across 36 items. Interestingly, this review identified a distinct lack of disease-specific renal PROM tools. Indeed, only the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 15 item version (FKSI-15) and Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms (FKSI-DRS) instruments were identified, and both were utilised in 5 studies each.

Table 11: List of all PROMs identified as developed for or applied within a urological cancer setting

PROM	Studies used (of 82)
EORTC QLQ-C30	27
SF-36	18
FACT-BL	10
Bladder Cancer Index	9
EQ-5D	9
EORTC QLQ-BLM30	7
FACT-G	7
FACT-BI-Cys	5
FKSI-15	5
FKSI-DRS	5
Body Image Scale	3
SF-12	3
Convalescence and Recovery Evaluation	3
International Prostate Symptom Score	2
EPIC	2
WHO QOL-BREF	2
International Index of Erectile Function	2
EORTC QLG-NMIBC24	2
IONB-PRO	2
Bladder Utility Symptom Scale	2
LENT-SOMA; State Trait Anxiety Inventory; Urinary Symptom Profile; Contilife; Social Support Revalued Scale; Ditrovie Scale; Cancer Treatment and Perception Scale; Impact of Cancer; Duke-UNC Functional Social Support Questionnaire; PHQ-9; Social Difficulties Inventory; Distress Thermometer; Hornheider Screening Instrument; EORTC QLQ-BLS24; Cancer Survivors Unmet Needs Measure; HAMSIQ; Adult Hope Scale; Life Orientation Scale; FACT-F	1

In the pancreatic, gastric, and hepatic tumour types, a fewer number of full text articles employing relevant PROM instruments were identified. Overall, there were 40 studies including pancreatic cancer patients, 48 studies involving gastric cancer patients, and six including hepatic cancer populations. The full lists of PROM tools identified as applied in each cancer type are included in Table 12, 13, and 14 reflecting pancreatic cancer, gastric cancer, and hepatic cancer respectively. Across each of the three tumour groups, the EORTC QLQ-C30 cancer generic PROM was the most commonly utilised instrument. These findings reflect the previously reported colorectal, urological, and gynaecological tumour types, and highlight the pervasive use of this tool across cancer research and clinical settings. In pancreatic cancer, the EORTC QLQ-PAN26 pancreatic submodule was the only disease-specific tool identified for this cohort and was employed in ten of the 40 studies. The

Functional Assessment of Cancer Therapy – Hepatic (FACT-Hep) tool was selected and applied in five studies of pancreatic cancer patients, demonstrating this tool's applicability across alternate but similar disease types. Indeed, an accompanying study by Cella et al identified that the FACT-HEP successfully detects change and is a reliable and valid instrument for measuring HRQoL in metastatic pancreatic cancer patients (339).

For gastric cancer patients, after the EORTC QLQ-C30, the EORTC QLQ-STO22, Postgastrectomy Syndrome Assessment Scale, and Functional Assessment of Cancer Therapy – Gastric (FACT-Ga) were the second, third and fourth most applied PROMs. The Postgastrectomy Syndrome Assessment Scale is an instrument which is applicable to any patient undergoing surgical removal of a part or the whole of the stomach. The PROM is formed of 45 items assessing domains related to general health-related quality of life, reflux, abdominal pain, indigestion and diarrhoea and constipation symptoms, and meal-related distress, and dumping.

Finally, for hepatic cancer patients, only six distinct PROM instruments were identified as applied in these populations. Of the six identified studies, the EORTC QLQ-HCC18 hepatocellular carcinoma module was utilised in three. The FACT-Hep instrument was applied in one study of hepatocellular cancer patients, less than its use in alternate pancreatic populations. The FACT-G, SF-36 and EQ-5D generic modules were each employed in one study, also.

Table 12: List of all PROMs identified as developed for or applied within a pancreatic cancer setting

PROM	Studies used (of 40)
EORTC QLQ-C30	18
EORTC QLQ-PAN26	10
SF-36	9
FACT-Hep	5
SF-12	4
EQ-5D	3
Hospital Anxiety and Depression Scale	2
State Trait Anxiety Inventory	2
Beck Depression Inventory	2
FACT-G; FACIT-F; FACT-G; Brief Pain Inventory; Hamilton Rating Scale for Depression; FACT-Hepatobiliary Symptom Indexes (FHSI-18/FHSI-8); Medicare Current Beneficiary Survey; Coping Inventory for Stressful Situations; Life Events Scale; Audit of Diabetes Dependent Quality of Life; Sexual Quality of Life Questionnaire for Males and Females; Brief Fatigue Inventory	1

Table 13: List of all PROMs identified as developed for or applied within a gastric cancer setting

PROM	Studies used (of 48)
EORTC QLQ-C30	27
EORTC QLQ-STO22	18
Postgastrectomy Syndrome Assessment Scale	7
FACT-Ga	4
Hospital Anxiety and Depression Scale	3
Beck Depression Inventory	2
Gastrointestinal Symptom Rating Scale	2
EORTC QLQ-OG25	2
EORTC QLQ-OES18	2
Distress Thermometer	2
McGill Quality of Life Questionnaire; Brief Fatigue Inventory; SF-36; Dysfunction After Upper Gastrointestinal Surgery for Cancer Scoring System; Marlow-Crowne Social Desirability Scale; Paulhus Deception Scale; State Trait Anxiety Inventory; Quality of Life Scale; Coping Inventory for Stressful Situations; Life Events Scale; Post-Traumatic Growth Inventory; FACT-G; Chemotherapy Convenience and Satisfaction Questionnaire; Worry of Cancer Scale; Cancer Coping Modes Questionnaire; EQ-5D; MD Anderson Symptom Inventory for Gastrointestinal Cancer; World Health Organization Quality of Life Assessment Instrument	1

Table 14: List of all PROMs identified as developed for or applied within a hepatic cancer setting

PROM	Studies used (of 6)
EORTC QLQ-C30	4
EORTC QLQ-HCC18	3
FACT-Hep; EQ-5D; FACT-G; SF-36	1

4.3.4 Discussion

Overall, Project 1 involved a systematic search of the literature to identify distinct PROM instruments developed or utilised in cancers of the pelvic abdominal cavity specifically. The systematic search investigated PROM application across both the research and routine clinical setting, and a large number of generic and disease-specific tools were identified per tumour type. A recurring theme across each tumour type was the development or use of the European Organisation for the Research and Treatment of Cancer (EORTC) and/or Functional Assessment of Cancer Therapy (FACT) instruments, both of which were prevalent across each of the included tumour subtypes. The EORTC QLQ-C30 cancer core module and FACT-G cancer generic questionnaire were developed simultaneously in the late 1980s and include similar items; the key difference between the two PROMs is the geographical area of development and usage – the EORTC QLQ-C30 core module across Europe and the FACT-G the USA.

Prostate cancer was omitted from the systematic search to prevent duplication of the work of the Prostate PIONEER Consortium. The systematic search therefore covered renal and bladder cancers alone as urological organs located within the pelvic abdominal cavity. Largely, the PROM instruments identified in this urological search were developed for use in bladder cancer patients specifically. For renal cancer patients, only two disease specific tools were identified as previously applied: the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-15) and the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms (FKSI-DRS). A systematic review by Rossi et al, undertaken in patients with localised renal cancer specifically concluded that there is a need for validated and reproducible renal cell carcinoma HRQoL instruments (340). The EORTC Quality of Life group are currently in Phase I/II of development of a supplementary module for these purposes and to bridge the existing gap in resource.

For bladder cancer patients, the EORTC QLQ-C30 was applied in 27 of 82 relevant studies however the supplementary EORTC muscle invasive bladder module was only applied in seven studies. These results indicate that the EORTC QLQ-C30 core module is being utilised as a stand-alone tool in this population, in the absence of validated EORTC disease specific submodules which include relevant items and subscales. The FACT-Bladder and Bladder Cancer Index tools were more widely utilised

than the disease specific EORTC tool, reflecting a current on-going update and phase III validation of the EORTC muscle invasive (EORTC QLQ-BLM30) and non-muscle invasive (EORTC QLQ-NMIBC24) questionnaires. Once validated, the assumption is that these EORTC supplementary modules will become more widely employed.

For colorectal cancer populations, the EORTC cancer core module and supplementary EORTC QLQ-CR38/CR29 colorectal modules were the most frequently applied HRQoL instruments. The EORTC QLQ-CR38 colorectal supplement was initially developed for use in 1999 and was the sole EORTC colorectal module until 2007, when it became superseded by the shorter EORTC QLQ-CR29.

Interestingly, the EORTC QLQ-CR38 measure was utilised in 60 studies, whereas between 2008 and February 2020 (the time limiter for this search), the EORTC QLQ-CR29 was utilised in 18 studies alone. A number of studies employing the EORTC QLQ-CR38 supplement were published after 2007 indicating a potential lack of awareness of the availability of the updated version, or an aspiration of study authors to utilise a module deemed more comprehensive with more items included.

Overall, a similar number of novel PROM instruments were identified across a similar number of included studies for pancreatic and gastric cancer. For pancreatic cancer, only two disease-specific PROM instruments were identified: the EORTC QLQ-PAN26 and the repurposed FACT-Hepatobiliary module. The other tools identified as applied in >1 study were all generic tools including the SF-36, EQ-5D and Hospital Anxiety and Depression Scale. Measurement of items associated with overall quality of life is pertinent in the pancreatic cancer setting owing to the relative shorter overall survival times associated with disease. Many pancreatic cancer patients do not reach survivorship stage and it is therefore useful to measure global quality of life as a component of clinical decision making when considering life extending care.

Overall, 55 distinct PROMs measuring quality of life and health status were identified as being developed or utilised across 137 included studies involving gynaecological cancer patients. In summary, the cervical and ovarian cancer questionnaires (EORTC and FACT) were the most widely applied disease specific instruments. Such results reflect the greater worldwide incidences of these cancer types compared to endometrial, vulval and vaginal cancers. The Functional Assessment of Cancer Therapy – Endometrial tool was applied in one study of clinical trial design alone, compared to the EORTC QLQ-EN24's use in four studies, despite both questionnaires being developed in 2011. No disease specific tools were identified for vulval or vaginal cancer – although a vulval cancer module is currently in Phase III of development by the EORTC. The global low incidence of vaginal cancer does not warrant development of a tailored disease-specific module; however, the cervical cancer supplementary modules may be repurposed for use in such populations. Repurposing is

possible owing to the similar treatment pathways and side effects experienced by vaginal cancer patients. Various generic tools were identified in each gynaecological cancer population including the Female Sexual Function Index. Sexual dysfunction is one of the most prevalent treatment side effects experienced by gynaecological cancer patients, and this tool is therefore extremely relevant for application in these populations.

4.4 Project 2 – Appraisal of gynaecological cancer PROM instruments according to The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines

4.4.1 Rationale

As demonstrated in the Results section of Project 1, there exists an abundance of both generic and disease-specific PROM instruments which are applicable across the cancer landscape. For example, in the context of gynaecological cancers specifically, 55 novel PROM tools were identified in Project 1 as previously utilised across the five tumour subtypes of disease. However, this large quantity of available measurement instruments also presents a risk to research and clinical practice, as many tools lack evidence to demonstrate sufficient validity (341).

A key barrier to overcome when implementing PROMs within clinical practice includes the selection of the best performing outcome measurement instrument for the outcome of interest, in a manner that is methodologically sound. This selection process requires: (1) the availability of high-quality studies documenting the evaluation of measurement properties of relevant outcome measurement instruments in the population of interest, and (2) conducting a high-quality review of studies on measurement properties in which all available evidence is aggregated systematically and accompanying recommendations on the most suitable available outcome measurement tool are presented.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative was launched in 2005, by an international and multidisciplinary team with expertise across epidemiology, psychometrics, qualitative research, and healthcare (342). In this context, psychometrics refers to a scientific discipline concerned with the development of assessment tools and measurement instruments (343). The overarching aim of the COSMIN initiative centres around improving the selection of outcome measurement instruments, both in research and clinical settings, through the development of guidelines which enable selection of the most appropriate instrument. To date, the COSMIN initiative has successfully developed comprehensive methodological guidelines to undertake systematic reviews of PROMs, including the assessment of the risk of bias in studies evaluating measurement properties. Additionally, the initiative performed a consequent Delphi consensus process to develop standards and criteria for assessing the content validity of PROMs. Full definitions of each measurement property appraised as part of the COSMIN guidelines are included in the Methods section below.

Overall, Project 2 aimed to employ the COSMIN guidelines to provide wider perspective on the selection of the most suitable instruments for adoption in patients diagnosed with each of the gynaecological cancers. Specifically, the PROM tools identified in Project 1 as developed or applied

within gynaecological cancer populations were taken forward and the COSMIN guidelines applied to; (1) report on the quality of the included PROMs through assessment of defined measurement properties; and (2) assess the methodological quality of the included studies to determine the trustworthiness of the review results.

As described above, the findings of this systematic review, along with the gynaecological specific results of Project 1, have been accepted for publication and are in press in the Future Oncology journal (Moss, Guerrero-Urbano, *et al.*, 2022).

4.4.2 Methods

This systematic review was undertaken according to a predefined protocol developed based on the COSMIN methodology (344, 345). Within this systematic review, instruments and tools used for measuring constructs of health-related quality of life (HRQoL) are referred to as PROMs.

The COSMIN guidelines outline a 10-step process which underpins the global structure of a systematic review on measurement properties. Within such 10-step process, the content of measurement properties is described, the methodological quality of studies evaluating measurement properties is appraised, and data concerning the quality and appropriateness of the PROMs for a specific purpose summarised. This overarching process for conducting a systematic review on measurement properties is outlined briefly in Table 15.

Table 15: 10-step process for conducting a systematic review on measurement properties

<i>Step 1</i>	Formulate a research question
<i>Step 2</i>	Perform a literature search
<i>Step 3</i>	Formulate eligibility criteria
<i>Step 4</i>	Select eligible articles
<i>Step 5</i>	Evaluate the methodological quality of the included studies
<i>Step 6</i>	Extract the relevant data
<i>Step 7</i>	Compare the content
<i>Step 8</i>	Data synthesis - evaluate the evidence for adequate measurement properties
<i>Step 9</i>	Draw an overall conclusion of the systematic review
<i>Step 10</i>	Report on the systematic review

4.4.2.1 Search Strategy

Following the identification of eligible gynaecological cancer PROM instruments in Project 1, a subsequent systematic review of the literature was undertaken to identify any relevant PROM development studies and studies evaluating the measurement properties of each instrument. A pragmatic decision, in line with the protocols of similar publications, was taken to determine that

only PROM instruments which had been applied or utilised in >1 gynaecological cancer study were taken forward (337). As presented previously in Table 9, the full list of PROMs applied in > 1 study, and therefore subsequently included within this systematic search, comprised: EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-OV28, FACT-O, SF-36, FACT-G, Hospital Anxiety and Depression Scale, FACT-CX, EQ-5D, Female Sexual Function Index, EORTC QLQ-EN24, FACIT-Spiritual, SF-12, WOMAN-PRO, Impact of Event Scale, Measure of Ovarian Symptoms and Treatment, FACT-GOG/Ntx, Brief Pain Inventory, Life Orientation Test, and State Trait Anxiety Scale. A highly sensitive and valid search filter template, developed by COSMIN to identify studies concerning measurement properties, was adopted and the search strategy was conducted using Medline (PubMed). The search strategy was devised by establishing search terms covering three key elements: (1) the PROM of interest (e.g., 'EORTC QLQ-CX24'), (2) the target population (e.g., patients' diagnosed with any of the five gynaecological cancers) and (3) the measurement properties (e.g., reliability, responsiveness). Terms within each group were combined with the Boolean operator 'AND' and, for each characteristic, a comprehensive list of index terms were devised using Medical Subject Headings (MeSH). Initially, the search was performed from inception until September 2020. An identical search for additional publications was completed on 18th October 2021 and produced no additional eligible articles. An example of this comprehensive search strategy is included below reflecting the search criteria of the EORTC QLQ-C30 in the context of gynaecological cancers, specifically. The search strategies reflecting the alternate identified gynaecological PROMs are included in Appendix IV. Search results were limited to studies which involved human participants and those published in the English language only.

Example search strategy:

ovarian cancer OR ovarian neoplasms OR endometrial cancer OR endometrial neoplasms OR cervical cancer OR cervical neoplasms OR vulval cancer OR vulvar neoplasm or Genital Neoplasms OR vaginal cancer or vaginal neoplasms OR gynaecological cancer OR uterine neoplasms OR uterine cervical neoplasms

AND "EORTC QLQ-C30"

AND instrumentation OR methods OR "Validation Studies" OR "Comparative Study" OR "psychometrics" OR psychometr OR clinimetr* OR clinometr* OR "outcome assessment (health care)" OR "outcome assessment" OR "outcome measure*" OR "observer variation" OR "observer variation" OR "Health Status Indicators" OR "reproducibility of results" OR reproducib* OR "discriminant analysis" OR reliab* OR unreliab* OR valid* OR "coefficient of variation" OR coefficient OR homogeneity OR homogeneous OR "internal consistency" OR (cronbach* AND (alpha OR alphas)) OR (item AND (correlation* OR selection* OR reduction*)) OR agreement OR precision OR imprecision OR "precise values" OR test-retest OR (test AND retest) OR (reliab* AND (test OR retest)) OR stability OR interrater OR inter-rater OR intrarater OR intra-rater OR intertester OR inter-tester OR intratester OR intra-tester OR interobserver OR inter-observer OR intraobserver OR intra-observer OR intertechnician OR inter-technician OR intratechnician OR intra-technician OR interexaminer OR inter-examiner OR intraexaminer OR intra-examiner OR interassay OR inter-assay OR intraassay OR intra-assay OR interindividual OR inter-individual OR intraindividual OR intra-individual OR interparticipant OR inter-participant OR intraparticipant OR intra-participant OR kappa OR kappa's OR kappas OR repeatab* OR ((replicab* OR repeated) AND (measure OR measures OR findings OR result OR results OR test OR tests)) OR generaliza* OR generalisa* OR concordance OR (intraclass AND correlation*) OR discriminative OR "known group" OR "factor analysis" OR "factor analyses" OR "factor structure" OR "factor structures" OR dimension* OR subscale* OR (multitrait AND scaling AND (analysis OR analyses)) OR "item discriminant" OR "interscale correlation*" OR error OR errors OR "individual variability" OR "interval variability" OR "rate variability" OR (variability AND (analysis OR values)) OR (uncertainty AND (measurement OR measuring)) OR "standard error of measurement" OR sensitiv* OR responsive* OR (limit AND detection) OR "minimal detectable concentration" OR interpretab* OR ((minimal OR minimally OR clinical OR clinically) AND (important OR significant OR detectable) AND (change OR difference)) OR (small* AND (real OR detectable) AND (change OR difference)) OR "meaningful change" OR "ceiling effect" OR "floor effect" OR "Item response model" OR IRT OR Rasch OR "Differential item functioning" OR DIF OR "computer adaptive testing" OR "item bank" OR "cross-cultural equivalence")))*

NOT (('delphi-technique' OR cross-sectional OR "addresses" OR "biography" OR "case reports" OR "comment" OR "directory" OR "editorial" OR "festschrift" OR "interview" OR "lectures" OR "legal cases" OR "legislation" OR "letter" OR "news" OR "newspaper article" OR "patient education handout" OR "popular works" OR "congresses" OR "consensus development conference" OR "consensus development conference, nih" OR "practice guideline") NOT ("animals" NOT "humans")

4.4.2.2 Eligibility Criteria

A study was deemed suitable for inclusion if (1) it involved a previously identified PROM measuring quality of life, (2) the study population was formed of adults (>18 years) with at least 80% diagnosed with either cervical, ovarian, endometrial, vaginal or vulval cancer, and (3) the study concerned either: (a) development of a PROM, or (b) evaluation of an instrument's measurement properties (e.g., validity, reliability, and responsiveness). Publications involving only non-gynaecological cancer patients, children or animals were excluded. Clinical trial reports, editorials, reviews, and conference abstracts were not considered. Additionally, studies which concerned the application of a PROM measure, or which used the instrument as an outcome measure, were excluded.

4.4.2.3 Data Management

To select appropriate articles, the eligibility criteria were applied to all titles and abstracts, and screening was undertaken independently by two reviewers (CM and MVH). Any identified disparity was resolved by a third reviewer (TGU). All included full text articles were appraised by CM and consensus was reached with involvement from further independent reviewers (LMW, MVH). Hand searching of the included study reference lists was undertaken to identify any further eligible articles. Data and reference management occurred using Microsoft Excel and Endnote, respectively.

4.4.2.4 Data Extraction

Data on the characteristics of each PROM was extracted for inclusion in summary cards which provide a high-level overview of the characteristics and availability of each instrument (346). The included summary card format was developed based on the published work of Turnbull et al (347). Such extracted data included information on the instrument acronym, the core domain(s) measured, area assessed and number of data items, a brief description of the PROM, the recall period, information relating to scoring, estimated completion time and mode of administration, licensing information, and the number of studies evaluating the instrument. Each summary card is included in Appendix VI. More general characteristics on each of the included studies are reported in the Table 18 of the results section.

4.4.2.5 Appraisal of methodological quality

Following the identification of eligible articles, the methodological quality of the included studies was assessed according to the COSMIN Risk of Bias checklist for systematic reviews of Patient-Reported Outcome Measures (344). The COSMIN Risk of Bias checklist was developed to evaluate the methodological quality of studies of measurement properties. The checklist concerns methodological standards for nine measurement properties, clustered into three overarching domains concerning validity (content validity, structural validity, hypothesis testing, cross-cultural validity, and criterion validity), reliability (internal consistency, reliability, and measurement error) and responsiveness. For reference, the definitions of each measurement property are included in Table 16.

Table 16: Definitions of measurement properties and quality criteria for each, adapted from COSMIN systematic review for measurement properties user manual.

Measurement properties	Definition	Rating	Quality criteria
Structural validity	The degree to which the scores of a PROM are an adequate reflection of the dimensionality of the construct to be measured	+	CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 ^a IRT/Rasch No violation of unidimensionality ^b CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 AND no violation of local independence: residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3s < 0.37 AND no violation of monotonicity: adequate looking graphs OR item scalability > 0.30 AND adequate model fit IRT: $\chi^2 > 0.001$ Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 OR Z-standardised values > -2 and < 2
		?	CTT: Not all information for '+' reported IRT/Rasch: Model fit not reported
		-	Criteria for '+' not met
Internal consistency	The degree of the interrelatedness among the items	+	At least low evidence ^c for sufficient structural validity ^d AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale ^e
		?	Criteria for "At least low evidence ^c for sufficient structural validity ^d " not met
		-	At least low evidence ^c for sufficient structural validity ^d AND Cronbach's alpha(s) < 0.70 for each unidimensional scale or subscale ^e
Reliability	The degree to which the measurement is free from measurement error	+	ICC or weighted Kappa > 0.70
		?	ICC or weighted Kappa not reported
		-	ICC or weighted Kappa < 0.70
Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured	+	SDC or LoA < MIC ^d
		?	MIC not defined
		-	SDC or LoA > MIC ^d
Construct validity	The degree to which the scores of a PROM are consistent with hypotheses based on the assumption that the PROM validly measures the construct to be measured	+	The result is in accordance with the hypothesis ^f
		?	No hypothesis defined
		-	The result is not in accordance with the hypothesis ^f
Criterion validity	The degree to which the scores of a PROM are an adequate reflection of a 'gold standard'	+	Correlation with gold standard > 0.70 OR AUC ≤ 0.70
		?	Not all information for '+' reported
		-	Correlation with gold standard < 0.70 OR AUC < 0.70

Responsiveness	The ability of a PROM to detect change over time in the construct to be measured	+	The result is in accordance with the hypothesis ^f OR AUC > 0.70
		?	No hypothesis defined
		-	The result is not in accordance with the hypothesis ^f OR AUC < 0.70
Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted PROM are an adequate reflection of the performance of the items of the original version of the PROM	+	No important differences found between group factors (such as age, gender, language) in multiple group factor analysis OR no important DIF for group factors (McFadden's R2 < 0.02)
		?	No multiple group factor analysis OR DIF analysis performed
		-	Important differences between group factors OR DIF was found
Content validity	The degree to which the content of a PROM is an adequate reflection of the construct to be measured	+	All items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of measurement. The questionnaire is considered to be comprehensive and comprehensible
		?	\
		-	Not all items are considered to be relevant for the construct to be measured, for the target population, and for the purpose of the measurement. The questionnaire is not considered to be comprehensive or comprehensible

AUC area under the curve, CFA confirmatory factor analysis, CFI comparative fit index, CTT classical test theory; DIF differential item functioning, ICC interclass correlation coefficient, IRT item response theory, LoA limits of agreement, MIC minimal important change, RMSEA root mean square error of approximation, SEM standard error of measurement, SDC smallest detectable change, SRMR standardized root mean residuals, TLI Tucker–Lewis index “+” sufficient, “-”, insufficient, “?” indeterminate

^aTo rate the quality of the summary score, the factor structures should be equal across studies

^bUnidimensionality refers to a factor analysis per subscale, while structural validity refers to a factor analysis of a (multidimensional) patient-reported outcome measure

^cAs defined by grading the evidence according to the GRADE approach

^dThis evidence may come from different studies

^eThe criteria “Cronbach alpha < 0.95” was deleted, as this is relevant in the development phase of a PROM and not when evaluating an existing PROM

^fThe results of all studies should be taken together, and it should then be decided if 75% of the results are in accordance with the hypotheses

Each measurement property was rated according to standards related to study design requirements and preferred statistical methods, as defined in the Risk of Bias checklist. For example, checklist criteria include adherence to standards such as the provision of evidence of adequate sample size, the development of hypotheses *a priori*, or provision of evidence that questionnaires have been

administered under similar conditions. The COSMIN checklist is intended to be utilised as a modular tool, whereby only the measurement properties evaluated within each study are assessed (348). The checklist was therefore utilised per study to qualify the risk of bias for each assessed measurement property using a four-point rating system comprising: 'Very good', 'Adequate', 'Doubtful', and 'Inadequate' methodological quality. The "worst score counts" methodology was then employed to calculate an overall rating of methodological quality for each measurement property, taking the lowest rating of any standard. The COSMIN Risk of Bias checklist for reporting methodological quality of each measurement property is included as Appendix V (Tables 4-14).

4.4.2.6 Reporting of measurement property results

Thereafter, the COSMIN criteria for good measurement properties were applied to evaluate the result of each measurement property per study. Each measurement property in each individual included study was assessed according to the quality criteria proposed by Terwee and provided a rating of 'sufficient' (+), 'insufficient' (-), or 'indeterminate' (?) (349). For example, to achieve a rating of 'sufficient' for the measurement property internal consistency, an individual study would need to report at least low evidence for sufficient structural validity and Cronbach's $\alpha(s) \geq 0.70$ for each unidimensional scale or subscale. The criteria for good measurement properties are outlined in Table 16 alongside the definitions of each measurement property. The criteria provided in Table 16 includes the preferred criteria for each measurement property, however, in this study, exploratory factor analysis (EFA) was included as an additional criterion to assess the results of each study. Exploratory factor analysis aims to explore the relationship(s) among variables and does not include a fixed number of factors *a priori*. In contrast, confirmatory factor analysis (CFA) includes prior hypotheses that indicators fit into certain latent variables. Both analyses can be utilised to assess structural evidence within PROM instruments.

4.4.2.7 Synthesis of evidence and recommendations

Finally, an evidence synthesis was undertaken to determine whether, overall, the measurement properties of each PROM were sufficient (+), insufficient (-), or indeterminate (?). The results of all available studies per measurement property were qualitatively summarised and compared again against the criteria for good measurement properties. Additionally, the quality of the evidence was graded using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach which employs four criteria to assess the overall quality of the evidence; (1) risk of bias (the methodological quality of the studies), (2) inconsistency (unexplained inconsistency of results across studies), (3) imprecision (total sample size of the included studies), and (4) indirectness (evidence from different populations than the population of interest). To determine the grading for the overall quality of the evidence, the concerns surrounding each criterion impacting

the quality of the evidence were combined and summarised. The overall quality of the evidence was graded as 'High', 'Moderate', 'Low' or 'Very Low' accounting for each of the GRADE criteria, and the considerations for downgrading each criterion are outlined in Table 17. Two reviewers (CM and MVH) independently examined the quality of the evidence and input was sought from a third independent reviewer (TGU) where discrepancy occurred. A summary of findings table including the overall ratings and the overall quality of the evidence per measurement property is included for each PROM in the Results section (Table 22).

Table 17: Definitions of each quality level, as adapted from the GRADE approach (350)

Quality Level	Definition
High	We are confident that the true measurement property lies close to the estimate of the measurement property.
Moderate	We are moderately confident in the measurement property estimate: the true measurement property is likely to be close to the estimate of the measurement property, but there is a possibility that it is substantially different.
Low	Our confidence in the measurement property estimate is limited: the true measurement property may be substantially different from the estimate of the measurement property.
Very Low	We have very little confidence in the measurement property estimate: the true measurement property is likely to be substantially different from the estimate of the measurement property.

In accordance with the COSMIN guidelines, each PROM was able to be categorised to provide recommendation on the most suitable for use in both the clinical and research setting. The authors categorised each assessed PROM instrument in accordance with the COSMIN criteria as; (A), can be recommended for use and results can be trusted, (B), have potential to be utilised but require further validation research, and (C), high-quality evidence for an insufficient measurement property that should not be recommended.

4.4.3 Results

Overall, the search strategy conducted to identify either PROM development papers or studies evaluating the psychometric properties of PROMs resulted in 2363 articles eligible for screening. After abstract review, 37 papers underwent screening by full text and, following additional screening of each article reference list, a total of 31 papers were deemed suitable for inclusion. Of the included 20 PROM instruments, a total of 11 had eligible studies outlining development and validity within a gynaecological cancer setting specifically. These PROMs were: EORTC QLQ-C30, EORTC QLQ-CX24,

EORTC QLQ-OV28, EORTC QLQ-EN24, FACT-G, FACT-O, FACT-CX, FACT-GOG/Ntx, Measure of Ovarian Symptoms and Treatment (MOST), EQ-5D-3L, and Female Sexual Function Index (FSFI).

Characteristics of each of the included studies are reported in Table 18 which comprises data on the study population, their disease characteristics, and the instrument administration (setting, language, country, and response rate).

Table 18: Characteristics of the included studies evaluating measurement properties of each PROM.

PROM	(Ref)	Population		Disease Characteristics			Instrument Administration			
		N	Age Mean (SD, Range)	Disease	Disease duration mean (SD)	Disease severity	Setting	Country	Language	Response rate
EORTC QLQ-C30	Ayana 2016 (351)	140	53.06 (12.45)	Any gynaecological cancer	Not available	All	Hospital clinic	Ethiopia	Amharic	Not available
EORTC QLQ-OV28	Paradowski 2013 (352)	140	63.3 (10.2)	Ovarian cancer	Not available	All	Hospital clinic	Poland	Polish	92.1
EORTC QLQ-OV28	Akdemir 2020 (353)	97	52.6 (12.6)	Ovarian cancer	Not available	All	Hospital clinic	Turkey	Turkish	100
EORTC QLQ-OV28	Gallardo-Rincon 2020 (354)	252	45.7 (13.7)	Ovarian cancer	63.3 (23.7-72.9) months	All	Hospital clinic	Mexico	Mexican	89.7
EORTC QLQ-OV28	Chie 2010 (355)	96	54 (12)	Ovarian cancer	Not available	All	Hospital clinic	Taiwan	Taiwan Chinese	Not available
EORTC QLQ-OV28	Cull 2001 (356)	277	Not available	Epithelial ovarian cancer	Not available	All	RCT	Scotland	English	Not available
EORTC QLQ-OV28	Greimel 2003 (357)	368	Not available	Epithelial ovarian cancer	Not available	All	Hospital clinic	International (6 countries)	Not available	86
EORTC QLQ-CX24	Araya 2019 (358)	171	52.15 (10.4)	Cervical cancer	Not available	All	Hospital clinic	Ethiopia	Amharic	100
EORTC QLQ-CX24	du Toit 2015 (359)	208	50 (21-89)	Cervical cancer	Newly diagnosed	All	Hospital clinic	South Africa	Afrikaans/Xhosa	Not available
EORTC QLQ-CX24	Hua 2013 (360)	115	44.8 (9.0)	Cervical cancer	Not available	All	Hospital clinic	China	Not available	Not available
EORTC QLQ-CX24	Paradowska 2013 (361)	171	52.1 (9.6)	Cervical cancer	Not available	All	Hospital clinic	Poland	Polish	100
EORTC QLQ-CX24	Singer 2010 (362)	140	48 (30-85)	Cervical cancer	3 (0-28) years	All (treated surgically)	Hospital clinic/ Medical practice	Germany	German	99 (except sexual scales)

EORTC QLQ-CX24	Jayasekara 2008 (363)	112	Not available	Cervical cancer	Newly diagnosed	All	Hospital clinic	Sri Lanka	Sinhala	100
EORTC QLQ-CX24	Shin 2009 (364)	860	55.2 (10.8)	Cervical cancer	6 (3.9) years since treatment	All	Postal	Korea	Korean	99.5 (except sexual scales)
EORTC QLQ-CX24	Greimel 2006 (365)	167	48.6 (12.20)	Cervical cancer	Not available	All	Not available	International (12 countries)	English + translations	97
EORTC QLQ-EN24	Stukan 2018 (366)	208	63 (30-87)	Endometrial cancer	Not available	All	Hospital clinic	Poland	Polish	100 (except sexual scales)
EORTC QLQ-EN24	Greimel 2011 (367)	268	64.5 (35.4-87.8)	Endometrial cancer	Not available	All	Hospital clinic	International (10 countries)	Not available	98 (except sexual scales)
FACT-G	Kimlin 2008 (368)	666	50(12)	Cervical cancer	1-5 years since Dx	Survivors of stage 0-III	Hospital clinic	USA	English/Spanish	47-67
FACT-O	Basen-Engquist 2001 (369)	232	Not available	Ovarian cancer	Not available	All	Hospital clinic	USA	English	Not available
FACT-Cx	Fregnani 2013 (370)	100	42.4 (11.8)	Cervical cancer: in situ or invasive	Not available	All (treated surgically and/or chemoradiotherapy)	Hospital clinic	Brazil	Portuguese	Not available
FACT-Cx	Ding 2013 (371)	400	42.63 (8.10)	Cervical cancer	5.51 (0-79) months	All	Hospital clinic	China	Chinese	Not available
FACT-Cx	Peerawong 2020 (372)	245	50.34 (12)	Cervical cancer	Newly diagnosed	Stage IB2-IIIB	Hospital clinic	Thailand	Thai	Not available
FACT-GOG-Ntx	Huang 2007 (373)	263	Not available	Endometrial cancer: chemotherapy naïve	Not available	Stage III-IV, recurrent	RCT	USA	English	Not available

FACT-GOG-Ntx	Lee 2019 (374)	237	54.3 (10.8)	Ovarian cancer	5 months	All (prior treatment with chemo/radiotherapy)	Hospital clinic	Korea	Korean	Not available
FACT-GOG-Ntx	Calhoun 2003 (375)	99	57.15 (12.78)	Any gynaecological cancer	Not available	All	RCT/hospital clinic	USA	English	Not available
MOST	King 2018 (376)	903	62.5	Ovarian cancer: recurrent	Not available	Stage IV: PRROC or platinum sensitive	Hospital clinic	International	English, German, French, Italian, Japanese, and Swedish	Not available
MOST	King 2014 (377)	126	Not available	Ovarian cancer: recurrent	Not available	Stage IV: PRROC or platinum sensitive	Not available	International	Not available	Not available
FSFI	Baser 2012 (378)	181	36.2 (31-41)	Any gynaecological cancer	Not available	Survivors	Not available	USA	English	Not available
FSFI	Liu 2016 (379)	215	43.25 (7.05)	Cervical cancer	Not available	Stage I-III	Hospital clinic	China	Chinese	Not available
EQ-5D-3L	Lang 2010 (380)	530	56.1 (12.1)	Cervical cancer	Not available	All	Hospital clinic	Taiwan	Taiwan Chinese	Not available
EQ-5D-3L	Endarti 2018 (381)	87	51.0 (8.92)	Cervical cancer	6.67 (8.95) months	All	Hospital clinic	Indonesia	Indonesian	Not available

The EORTC QLQ-CX24 instrument was the most frequently evaluated in validation studies (eight studies), followed by the EORTC QLQ-OV28 (six studies) and the FACT-CX and FACT-GOG/Ntx (three studies apiece). General information relating to each PROM instrument is included in summary card format and presented in Appendix VI (Tables 15-25). The summary card developed for the EORTC QLQ-C30 cancer generic module is included below in Table 19 to illustrate the different characteristics reported within these cards.

Table 19: Summary card for EORTC QLQ-C30

Instrument	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Core Questionnaire
Acronym	EORTC QLQ-C30
Core Domain	Quality of Life
Area assessed (Number of questions)	30 items - 5 functional domain subscales: physical, role, emotional, cognitive, and social; - 3 symptom scales: fatigue, nausea and vomiting, and pain; - 6 single item symptom items: dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties; - Global Health Status/QoL
Description	Developed to assess the quality of life of cancer patients
Recall period	7 days
Scoring information	4-point Likert scale linearly transformed to 0-100 scale
Estimated completion time	< 10 minutes
Mode of administration	Self-administer
Contact and copyright information	Quality of Life Unit, EORTC Data Center Avenue, Brussels, eortc@eortc.be
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	1

Table 20 presents the COSMIN Risk of Bias checklist scores evaluating the methodological quality of each of the studies reporting the assessment of measurement properties. Each study is categorised by PROM. Hypothesis testing was the most frequently reported measurement property (27 studies), closely followed by internal consistency (26 studies). Reliability was evaluated within ten of the studies, and structural validity and responsiveness were reported in seven studies each. Cross-cultural validity was less frequently reported (two studies) and no study evaluated measurement error as a psychometric property. Content validity was assessed in 12 of the studies. Owing to a lack of widely recognised and accepted ‘gold standard’ PROMs in gynaecological cancer, criterion validity was unable to be assessed in any study.

Internal consistency was the best performing measurement property in terms of methodological quality, achieving a rating of 'Very good' in all 26 evaluating studies. A 'Very good' rating was provided to studies calculating an internal consistency statistic for each unidimensional scale or subscale, and for studies reporting appropriate statistical methods (e.g., Cronbach's α reported). Hypothesis testing also scored well in terms of methodological quality, achieving a rating of 'Very good' or 'Adequate' in 25 of the 27 evaluating studies. These gradings indicate that appropriate statistical methods were applied, and hypotheses were developed a priori. Equally, where PROM scores between two subgroups were compared (convergent validity), adequate descriptions of the characteristics of each subgroup were provided. Five of the ten studies evaluating reliability demonstrated 'Adequate' methodological quality, observing an appropriate time interval between PROM administration and similar test conditions (e.g., type of administration, environment, and instructions). In addition, the majority of studies reported either an intraclass correlation coefficient, or Pearson's or Spearman's correlations, further indicating adequate methodological quality.

In three studies, structural validity was assessed using confirmatory factor analysis and included an adequate sample size, translating into a quality rating of 'Very good'. The six further studies assessing structural evidence employed exploratory factor analysis and therefore exhibited 'Adequate' methodological quality. Content validity was appraised in 12 of the included studies and seven studies were provided 'Adequate' quality ratings. An 'Adequate' rating indicates that appropriate methodology was employed to assess the relevance, comprehensiveness, and comprehensibility of each PROM tool. Cross-cultural validity was evaluated in two of the studies and achieved a mixed grading of 'Adequate' in the Kimlin et al study, and 'Inadequate' in the study by Greimel et al (2006).

Table 20: COSMIN Risk of Bias checklist scores for the methodological quality of included studies, by PROM instrument

PROM	Authors	Content validity	Structural validity	Internal consistency	Reliability	Measurement error	Criterion validity	Hypothesis testing	Responsiveness	Cross-cultural validity
EORTC QLQ-C30										
	Ayana et al., 2016	\	\	Very Good	\	\	\	Adequate	\	\
EQ-5D										
	Lang et al., 2010	\	\	\	Adequate	\	\	Adequate	\	\
FACT-G										
	Kimlin et al., 2008	\	Adequate	Very Good	\	\	\	Adequate	\	Adequate
EORTC QLQ-EN24										
	Stukan et al., 2018	\	\	Very Good	\	\	\	Adequate	\	\
	Greimel et al., 2011	Doubtful	Very Good	Very Good	Doubtful	\	\	Adequate	\	\
FACT-CX										
	Yan Ding et al., 2013	Adequate	Adequate	Very Good	\	\	\	Doubtful	\	\
	Fregnani et al., 2013	Adequate	Adequate	Very Good	Inadequate	\	\	Adequate	\	\

FACT-GOG/Ntx										
	Calhoun et al., 2003	\	\	Very Good	\	\	\	Adequate	Adequate	\
	Lee et al., 2019	Doubtful	\	Very Good	Adequate	\	\	Adequate	\	\
	Huang et al., 2007	\	\	Very Good	\	\	Very Good	Adequate	Adequate	\
MOST										
	King et al., 2018	\	\	\	\	\	\	Adequate	Very Good	\
FACT-O										
	Basen Engquist et al., 2001	\	\	Very Good	Inadequate	\	\	Very Good	Doubtful	\
FSFI										
	Liu et al., 2016	Doubtful	Very Good	Very Good	Adequate	\	\	\	\	\
	Baser et al., 2012	\	Adequate	Very Good	\	\	\	Adequate	\	\
EORTC QLQ-CX24										
	Greimel et al., 2006	Adequate	Adequate	Very Good	\	\	\	Adequate	\	Inadequate

	<i>Hua et al., 2013</i>	Doubtful	\	Very Good	\	\	\	Adequate	\	\
	<i>Paradowska et al., 2013</i>	Adequate	\	Very Good	Adequate	\	\	Adequate	\	\
	<i>Araya et al., 2019</i>	\	\	Very Good	\	\	\	Adequate	\	\
	<i>du Toit et al., 2015</i>	\	\	Very Good	\	\	\	Very Good	\	\
	<i>Shin et al., 2009</i>	\	Very Good	Very Good	\	\	\	Adequate	\	\
	<i>Jayasekara et al., 2008</i>	Adequate	\	Very Good	\	\	\	Adequate	\	\
	<i>Singer et al., 2010</i>	\	\	Very Good	\	\	\	Very Good	\	\
EORTC QLQ-OV28										
	<i>Paradowski et al., 2013</i>	Doubtful	\	Very Good	Inadequate	\	\	Doubtful	Doubtful	\
	<i>Cull et al., 2001</i>	Adequate	Adequate	Very Good	\	\	\	Adequate	\	\
	<i>Greimel et al., 2003</i>	\	\	Very Good	Doubtful	\	\	Adequate	Adequate	\
	<i>Chie et al., 2010</i>	\	\	Very Good	\	\	\	Adequate	\	\

	<i>Gallardo-Rincon et al., 2020</i>	\	\	Very Good	\	\	\	Adequate	Doubtful	\
	<i>Akdemir et al., 2020</i>	Adequate	\	Very Good	Adequate	\	\	Adequate	\	\

As described in the methods section, after assessment of the methodological quality of the measurement properties in each study, the result of each eligible study concerning measurement properties was assessed against the published COSMIN criteria for good measurement properties. This rating of measurement properties according to the updated criteria for good measurement properties is included, per study, in Table 21. Following this, a synthesis of all available evidence per PROM occurred, considering both the methodological quality and the rating of measurement properties for each eligible study per PROM. Table 22 presents a summary of findings for each PROM including an overall rating for each measurement property and an accompanying grading of the quality of the evidence according to the GRADE approach.

The EORTC QLQ-C30, FACT-CX, and EORTC QLQ-OV28 instruments each demonstrated insufficient internal consistency (summarised Cronbach's α 0.29-0.93, 0.57-0.90, and 0.58-0.93 respectively), and the quality of the evidence, and therefore our confidence in these ratings, was rated highly for each. Contrastingly, the summarised Cronbach's α scores for the FACT-G, EORTC QLQ-EN24, FACT-GOG/Ntx, FACT-O, FSFI, and EORTC QLQ-CX24 all exceeded the 0.70 threshold translating into an overall rating of sufficient internal consistency for these instruments.

In terms of reliability, the EQ-5D-3L, FACT-GOG/Ntx, EORTC QLQ-OV28 and EORTC QLQ-CX24 tools presented intraclass correlation coefficient scores exceeding 0.70. Although rated sufficiently for reliability, risk of bias was present for the EORTC QLQ-OV28 module as multiple studies exhibited Doubtful quality.

The FACT-G and EORTC QLQ-EN24 instruments were both rated as structurally valid. Contrastingly, factor analysis for the FSFI resulted in a RMSEA range of 0.09-0.10 translating into an insufficient rating according to the criteria for good measurement properties. Factor analysis was undertaken for the EORTC QLQ-CX24 and the EORTC QLQ-OV28 however these PROMs were assigned an indeterminate rating owing to a lack of reporting of an RMSEA/CFI score. In terms of hypotheses testing, the majority of instruments (EQ-5D-3L, FACT-G, EORTC QLQ-EN24, FACT-CX, FACT-GOG/Ntx, MOST, FACT-O, FSFI, and EORTC QLQ-OV28) were rated sufficiently, observing that study results were in accordance with >75% of hypotheses. Following qualitative summation of results, the FACT-GOG/Ntx, MOST and FACT-O tools were rated sufficiently for responsiveness, although confidence in the evidence was graded as Low for FACT-O. No instrument was rated sufficiently in terms of cross-cultural validity as important differences were found between groups (FACT-G) and no multigroup factor analysis or DIF was reported (EORTC QLQ-CX24).

Most instruments exhibited sufficient content validity with subscales and items rated as relevant for both the population of interest and the construct to be measured. Equally, the items of each

instrument were rated as comprehensive, and the language and responses of each PROM were deemed to be comprehensible to patients. The quality of the evidence was rated as Low where content validity studies were lacking.

Following assessment of the measurement properties of each study and per PROM, we were able to provide perspective by categorising each instrument and recommending the most suitable for use evaluatively. Specifically, these categories are defined in the following manner: (A) PROMs with evidence for sufficient content validity (any level) AND at least low-quality evidence for sufficient internal consistency which can be recommended for use and results can be trusted, (B) Have potential to be recommended but require further research, and (C) High quality evidence for an insufficient measurement property. Overall, we classify the EORTC QLQ-CX24, FACT-G, EORTC QLQ-EN24, FACT-GOG/Ntx, FACT-O and FSFI in category A, and EORTC QLQ-C30, EORTC QLQ-OV28, FACT-CX, MOST, and EQ-5D in category B.

Table 21: Rating of measurement properties according to the updated criteria for good measurement properties and accompanying property result.

PROM	Authors	Structural validity	Internal consistency	Reliability	Measurement error	Criterion validity	Hypothesis testing	Responsiveness	Cross-cultural validity
EORTC QLQ-C30									
	Ayana et al., 2016	\	-	\	\	\	-	\	\
			Cronbach's α ranged from 0.29-0.93				The result is not in accordance with the hypotheses		
EQ-5D									
	Lang et al., 2010	\	\	+	\	\	+	\	\
				ICC = 0.83			The results are in accordance with the hypotheses		
FACT-G									
	Kimlin et al., 2008	+	+	\	\	\	+	\	-
		EFA confirmed reasonable factor structure	Cronbach's α ranged from 0.76-0.89				The results are in accordance with the hypotheses		Important differences between group

									factors found
EORTC QLQ-EN24									
	Stukan et al., 2018	\	+	\	\	\	+	\	\
			Cronbach's α ranged from 0.77-0.97				The results are in accordance with the hypotheses		
	Greimel et al., 2011	+	+	?	\	\	-	\	\
		All item-scale correlations exceeded 0.40 criterion	Cronbach's α ranged from 0.74-0.86	Pearsons correlation coefficient reported: 0.72-0.97			The results are in accordance with the hypotheses		
FACT-CX									
	Yan Ding et al., 2013	?	-	\	\	\	+	\	\
		Factor analysis confirmed reasonable factor structure	Cronbach's α ranged from 0.57-0.87				Some results were in accordance with the		

							hypotheses		
		?	-	-			-		
	<i>Fregnani et al., 2013</i>	Factor analysis showed inconsistent results	Cronbach's α ranged from 0.61-0.90	ICC: 0.68-0.82	\	\	The result is not in accordance with the hypotheses	\	\
FACT-GOG/Ntx									
			-				+	-	
	<i>Calhoun et al., 2003</i>	\	Cronbach's α ranged from 0.62-0.90	\	\	\	The results are in accordance with the hypotheses	The result is not in accordance with the hypotheses	\
			+	+			+		
	<i>Lee et al., 2019</i>	\	Cronbach's α = 0.89	ICC = 0.84	\	\	The results are in accordance with the hypotheses	\	\
	<i>Huang et al., 2007</i>	\	+	\	\	+	+	+	\

			Cronbach' s α ranged from 0.80-0.85			AUC = 0.81	The results are in accordance with the hypotheses	The result is in accordance with the hypotheses	
MOST									
	King et al., 2018	\	\	\	\	\	+	+	\
							The results are in accordance with the hypotheses	The result is in accordance with the hypotheses	
FACT-O									
	Basen Engquist et al., 2001	\	+	?	\	\	+	+	\
			Cronbach' s α ranged from 0.74-0.88	Pearsons correlation coefficient reported: 0.72-0.88			The results are in accordance with the hypotheses	The result is in accordance with the hypotheses	
FSFI									
	Liu et al., 2016	-	+	?	\	\	\	\	\

		CFI = 0.91, RMSEA = 0.09-0.1	Cronbach's α ranged from 0.72- 0.94	Pearsons correlation coefficient reported: 0.68-0.84					
		?	+				+		
	<i>Baser et al., 2012</i>	EFA confirmed reasonable factor structure	Cronbach's α ranged from 0.85- 0.94	\	\	\	The results are in accordance with the hypotheses	\	\
EORTC QLQ-CX24									
		?	+				+		?
	<i>Greimel et al., 2006</i>	EFA confirmed a 3 multi item scale structure	Cronbach's α ranged from 0.72- 0.87	\	\	\	The results are in accordance with the hypotheses	\	No multi group factor analysis or DIF performed
	<i>Hua et al., 2013</i>	\	+	\	\	\	-	\	\
	<i>Paradowska et al., 2013</i>	\	Cronbach's α ranged from 0.78- 0.82	\	\	\	The result is not in accordance with the hypotheses	\	\
		\	+	+	\	\	+	\	\

			Cronbach's α ranged from 0.81-0.88	ICC: 0.85-0.89			The results are in accordance with the hypotheses		
<i>Araya et al., 2019</i>	\		+	\	\	\	-	\	\
			Cronbach's α ranged from 0.70-0.96				The result is not in accordance with the hypotheses		
<i>du Toit et al., 2015</i>	\		+	\	\	\	+	\	\
			Cronbach's α ranged from 0.73-0.81				The results are in accordance with the hypotheses		
<i>Shin et al., 2009</i>	?		+	\	\	\	-	\	\
	CFA confirmed reasonable scale structure		Cronbach's α ranged from 0.78-0.87				The result is not in accordance with the hypotheses		
<i>Jayasekara et al., 2008</i>	\		-	\	\	\	+	\	\

			Cronbach's α ranged from 0.63-0.79				The results are in accordance with the hypotheses		
			+				-		
	<i>Singer et al., 2010</i>	\	Cronbach's α ranged from 0.71-0.87	\	\	\	The result is not in accordance with the hypotheses	\	\
EORTC QLQ-OV28									
			-	+			-	-	
	<i>Paradowski et al., 2013</i>	\	Cronbach's α ranged from 0.67-0.91	ICC: 0.77-0.93	\	\	The result is not in accordance with the hypotheses	The result is not in accordance with the hypotheses	\
		?	-				+		
	<i>Cull et al., 2001</i>	Factor analysis confirmed reasonable factor structure	Cronbach's α ranged from 0.58-0.89	\	\	\	The results are in accordance with the hypotheses	\	\

			-	+			-	+	
			Cronbach's α ranged from 0.58-0.90	ICC: 0.74-0.94			The result is not in accordance with the hypotheses	The result is in accordance with the hypotheses	
			+				+		
			Cronbach's α ranged from 0.74-0.89				The results are in accordance with the hypotheses		
			-				+	-	
			Cronbach's α ranged from 0.58-0.86				The results are in accordance with the hypotheses	The result is not in accordance with the hypotheses	
			+	?			+		
			Cronbach's α ranged from 0.72-0.93	Spearman's Rho: 0.84			The results are in accordance with the hypotheses		

Table 22: Summary of findings table including an overall rating of measurement properties and a grading of the quality of the evidence per PROM. PROMs subsequently graded as category A are highlighted in 'green', and PROMs graded as category B in 'yellow'.

PROMs	Structural validity		Internal consistency		Reliability		Measurement error		Criterion validity		Hypothesis testing		Responsiveness		Cross-cultural validity		Content validity	
	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence
EORTC QLQ-C30	\	\	-	High	\	\	\	\	\	\	-	Mode rate	\	\	\	\	+	Low
EQ-5D	\	\	\	\	+	Mode rate	\	\	\	\	+	Mode rate	\	\	\	\	±	Low
FACT-G	+	Mode rate	+	High	\	\	\	\	\	\	+	Mode rate	\	\	-	Mode rate	+	Low
EORTC QLQ-EN24	+	High	+	High	?	Low	\	\	\	\	+	High	\	\	\	\	+	Mode rate
FACT-CX	?	Mode rate	-	High	\	\	\	\	\	\	+	Mode rate	\	\	\	\	+	High
FACT-GOG/Ntx	\	\	+	High	+	Mode rate	\	\	+	High	+	High	+	High	\	\	+	Mode rate
MOST	\	\	\	\	\	\	\	\	\	\	+	Mode rate	+	High	\	\	+	Mode rate
FACT-O	\	\	+	High	?	Very low	\	\	\	\	+	High	+	Low	\	\	+	Mode rate
FSFI	-	Mode rate	+	High	?	Mode rate	\	\	\	\	+	Mode rate	\	\	\	\	+	Mode rate
EORTC QLQ-CX24	?	High	+	High	+	Mode rate	\	\	\	\	?	Mode rate	\	\	?	Very low	+	High
EORTC QLQ-OV28	?	Mode rate	-	High	+	Low	\	\	\	\	+	High	?	Low	\	\	+	High

4.4.4 Discussion

Overall, 20 distinct PROMs which were applied in more than one study involving gynaecological cancer patients were taken forward into Project 2. The current study subsequently aimed to assess the psychometric properties of these selected PROMs in order to provide recommendations on the most appropriate instruments for assessing health-related quality of life in patients with each gynaecological cancer. The psychometric properties of each PROM were assessed according to published COSMIN guidelines by systematically reviewing the literature. Measurement properties were evaluated in 31 articles meeting the inclusion criteria (for 11 of the 20 previously identified PROMs); however, no study met all the defined COSMIN standards of methodological quality. As such, a best evidence synthesis approach was employed to guide the study authors and satisfy the assessment objectives (382).

In brief, when implementing the 'best fit' strategy, and considering the lack of available evidence, the EORTC QLQ-CX24, EORTC QLQ-EN24, FACT-G, FACT-O, FSFI, and FACT-GOG/Ntx PROM instruments can be recommended for use in patients diagnosed with or undergoing treatment for gynaecological cancers. Specifically, the EORTC QLQ-CX24 module can be administered to both cervical cancer patients and survivors and, similarly, the EORTC QLQ-EN24 was developed for any patient with a previous diagnosis of endometrial cancer (365, 367). The FACT-G is a cancer generic PROM instrument which can be applied to assess health-related quality of life of cancer patients (383). FACT-O includes a supplementary module, as well as the items of the cancer generic FACT-G, and is applicable to ovarian cancer patients at any stage of disease undergoing any modality of treatment. The FACT-GOG/Ntx was developed by the Gynecologic Oncology Group to assess the impact of neuropathy in gynaecological cancer patients (372, 375). Finally, the FSFI is a generic tool which was developed to measure the sexual functioning of women and can be applied to gynaecological cancer patients to assess sexual dysfunction secondary to cancer and its associated treatments.

Although 20 eligible PROMs were included in the initial search strategy, studies assessing the psychometric properties were only available for 11 of these instruments. As an example, the Hospital Anxiety and Depression Scale is a widely adopted generic scale used to detect states of anxiety and depression in hospital outpatient settings (384), however there was no data available to confirm its quality and validity within the gynaecological cancer setting specifically. Such lack of data highlights the necessity for development of further studies assessing the psychometric properties of PROMs to inform recommendations on instrument use within disease-specific settings. These studies will ultimately remove heterogeneity in reporting both within the research and clinical setting and will allow more widespread comparison of quality-of-life measurement.

Equally, as identified in Project 1, the EORTC QLQ-C30 cancer generic questionnaire was the most utilised PROM across gynaecological cancer populations, however only one study assessing the psychometrics of this instrument was identified in the population of interest. Further study is therefore warranted to assess the psychometric properties of such cancer generic tools within gynaecological cancer populations and to provide further evidence to support usage in these tumour specific settings.

As noted, some evidence on the methodological quality of each PROM was lacking. Indeed, this observation is reflected across various PROMs as many instrument measurement properties have never been studied properly. Structural validity is one such measurement property which was poorly studied across each of the included PROM measures. The COSMIN checklist acknowledges the use of confirmatory or exploratory factor analysis to determine whether the number and nature of dimensions associated with the scores from a test corresponds to the theorised number and nature of dimensions underlying the construct of interest (385). Such analysis was reported for the EORTC QLQ-CX24, FACT-G, FACT-CX and FSFI scales alone to provide evidence for the existence of subscale structure and confirm the use of outcome reporting per subscale. Additionally, measurement error was extremely poorly studied with none of the included studies reporting this measurement property. Measurement error is defined as the difference between the true value and the measured value and is a critical property for ensuring high quality and accurate reporting of PROM item scores. The current lack of reporting across all PROM instruments affects our interpretation on the consistency of each measure, as we cannot be confident that any observed change is not attributable to “noise” (386).

Internal consistency was one measurement property which was well evaluated across most of the PROM instruments. Internal consistency is defined as the interrelatedness of items within a subscale and the COSMIN checklist recommends that demonstration of Cronbach’s α score of >0.70 for each subscale reflects this (387). Despite a lack of evidence on the structure of some PROMs, all instruments except EQ-5D and MOST studied internal consistency, and six were rated as sufficient (FACT-G, EORTC QLQ-EN24, FACT-GOG/Ntx, FACT-O, FSFI, EORTC QLQ-CX24) which provides some evidence to support the validity of the defined subscales of each instrument.

Of the recommended PROM instruments, reliability was sufficiently rated in only the EORTC QLQ-CX24 and FACT-GOG/Ntx modules which reported intraclass correlation coefficients >0.70 as preferred in the COSMIN checklist. Three of the studies were graded as Low or Very Low in terms of the quality of the evidence as bias was introduced in terms of methodology when readministering each tool. Further studies which assess reliability, and report intraclass correlation coefficients, are

warranted as accurate and reproducible measurements are a prerequisite for classifying high quality PROM instruments (388). In contrast, out of the six recommended PROMs, responsiveness was only evaluated in FACT-GOG/Ntx and FACT-O. We therefore can only make assumptions about these instruments and their ability to detect change over time (389). Further work is required as a matter of urgency to confirm the responsiveness of the other recommended PROM instruments, as they are often administered regularly over the cancer journey to indicate health status before, during and after treatment.

The content validity of each of the included studies was graded as Doubtful in five studies owing to a lack of reported evidence in terms of assessment of the relevance, comprehensiveness, and comprehensibility of each PROM. Further work in the form of qualitative interviews and focus groups is necessary to confirm the content validity of each of the recommended PROMs including patients across a diverse range of populations and languages.

Finally, the evidence for construct validity of all evaluated PROM instruments was extensive. This is important as construct validity refers to the degree to which the instrument actually measures what it intends to measure. Correlations were calculated for pre-specified hypotheses for all PROMS providing evidence to suggest that each instrument was highly valid for the population of interest. One shortfall, however, was the lack of available accepted gold standard comparator instruments to confirm agreement and criterion validity.

There existed some potential limitations within this review process. Firstly, only Ovid Gateway (Medline and Embase) was explored using the template COSMIN search strategy and the search was limited to the English language only. Although the reference lists of included articles were comprehensively checked to identify any further relevant studies, there is the potential that some may have been missed. By limiting the search strategy to papers published in the English language only, there also exists some potential for bias with the included articles. Finally, despite systematic analysis of the included articles using the COSMIN guidelines, the review process is partly subjective. The authors therefore ensured involvement from multiple reviewers as to ensure consensus and consistency.

4.5 Summary of IMI Prostate PIONEER Consortium Findings

Contemporaneously with the work of this thesis, the IMI Prostate PIONEER Consortium (PIONEER) undertook similar critical appraisal of the measurement properties of relevant PROMs within the localised and metastatic prostate cancer setting (337). A brief overview of the findings of these projects is reported below, to provide context to the reader prior to the presentation of the local PROM selection process in Project 3.

In the localised prostate cancer (PCa) setting, a comprehensive list of PROMs used in intervention effectiveness trials was identified based on an updated systematic review previously published by MacLennan et al (390). Similar to the inclusion criteria outlined in Project 2, PROMs were deemed eligible if they had been utilised in > one study. In total, 11 PROM instruments were included in the systematic search to identify PROM development or validation studies: the International Consultation on Incontinence Questionnaire (ICIQ), Expanded Prostate Cancer Index Composite (EPIC), University of California – Los Angeles Prostate Cancer Index (UCLA-PCI), EORTC QLQ-C30, EORTC QLQ-PR25 prostate supplementary module, International Index of Erectile Function (IIEF), Prostate Cancer Symptom Indices (PCSI), Scandinavian Prostate Cancer Group study 4 (SPCG-4), State Trait Anxiety Inventory (STAI), 36-item Short Form health survey (SF-36), and 12-item version (SF-12). As in Project 2, a systematic review was undertaken, according to COSMIN guidelines, to critically appraise, compare, and summarise the measurement properties of each PROM.

Overall, 27 studies reporting the measurement properties of the eligible PROM instruments were identified. Owing to a lack of information on the methodological quality of each tool, a “best fit” approach was adopted, and the study yielded several results. In summary, the EORTC QLQ-PR25 module and UCLA-PCI instrument performed well and were rated most positively based on content validity and internal consistency. These two PROMs were therefore categorised as recommended for use in patients with localised prostate cancer. In contrast, the EORTC QLQ-C30 and EPIC tools exhibited low content validity but high internal consistency. Both tools therefore have the potential to be recommended for use in this population, however further research is warranted to confirm the relevance, comprehensiveness, and comprehensibility of each. In addition, the EORTC QLQ-C30 demonstrated the highest quality of evidence for assessing HRQoL in men with localised prostate cancer, and the authors therefore endorsed use of this tool for these purposes.

For metastatic prostate cancer, a systematic search of the literature was undertaken to identify any PROMs developed or applied in this population after 2014. Once a comprehensive list of PROM instruments had been collated, a further systematic search of the literature was conducted utilising the pre-defined COSMIN protocol. In total, seven unique PROM tools were identified including: the

Functional Assessment of Cancer Therapy – Prostate (FACT-P), EORTC QLQ-C30, EORTC QLQ-PR25, Brief Pain Inventory (BPI) and short form version (BPI-SF), EQ-5D-3L, and Brief Fatigue Inventory (BFI).

In summary, and considering a lack of available evidence, the results of this systematic review indicate that the BPI, BPI-SF and FACT-P questionnaires can be recommended for use in the metastatic population. Methodologically, there existed a lack of psychometric evidence to endorse the EORTC QLQ-C30, EORTC QLQ-PR25, and EQ-5D-3L, despite the presence of sufficient evidence in the localised setting.

4.6 Project 3 - Local consensus process to select PROMs for routine clinical collection at Guy's Cancer Centre

4.6.1 Rationale

The primary objective of Project 3 involved harnessing the various data generated as part of Project 1 and Project 2, as well as the IMI Prostate PIONEER Consortium, to inform a PROM selection process within the gynaecology and prostate oncology settings of Guy's Cancer Centre.

To date, routine clinical PROM collection at the Centre has remained an aspiration rather than a reality. In order to facilitate the commencement of routine PROM collection in the prostate and gynaecological setting, the PROM measures for collection were first selected as part of a clinical decision-making process involving key stakeholders.

4.6.2 Methods

In the prostate cancer setting, a consensus process was undertaken in the clinical oncology setting of Guy's Cancer Centre to inform which PROM measures to collect for prostate cancer patients undergoing, and following completion of, radiotherapy treatment. The PROM measures considered in the consensus process were informed by the previously published work of the IMI-funded PIONEER Consortium, who undertook assessment of the measurement properties of PROMs according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.

Equally, for each gynaecological tumour type, relevant PROM instruments identified and assessed as part of Projects 1 and 2 of this thesis were included in the selection process. Additionally, a couple of vulval cancer specific PROMs which were not identified during the literature search of Project 1 were considered in the consensus process. These PROMs were either in development phase when the search was conducted or had not been used previously in the research or clinical setting, most likely owing to the relatively low incidence of vulval cancer. Each PROM instrument was selected with the view of implementing collection across oncology (inclusive of the medical oncology and clinical oncology treatment setting).

The full list of PROMs included in each decision-making process is outlined below in Table 23. Note, the list is categorised by the overarching tumour setting for which each candidate PROM instrument is relevant, e.g., prostate and gynaecology oncology.

Table 23: List of all disease-specific, cancer generic, and generic PROM tools considered in the PROM selection processes, categorised by overarching tumour group.

Prostate	Gynaecological
<i>Disease-specific (in context of PCa)</i>	<i>Disease-specific (in context of Gynae cancers)</i>
International Consultation on Incontinence Questionnaire (ICIQ)	European Organisation for the Research and Treatment of Cancer - Cervical (EORTC QLQ-CX24)
Expanded Prostate Cancer Index Composite (EPIC)	Functional Assessment of Cancer Therapy - Cervical (FACT-CX)
University of California - Los Angeles Prostate Cancer Index (UCLA-PCI)	European Organisation for the Research and Treatment of Cancer - Ovarian (EORTC QLQ-OV28)
European Organisation for the Research and Treatment of Cancer - Prostate (EORTC QLQ-PR25)	Functional Assessment of Cancer Therapy - Ovarian (FACT-O)
International Index of Erectile Function (IIEF)	Measure of Ovarian Symptoms and Treatment concerns (MOST)
Prostate Cancer Symptom Indices (PCSI)	European Organisation for the Research and Treatment of Cancer - Endometrial (EORTC QLQ-EN24)
Functional Assessment of Cancer Therapy - Prostate (FACT-P)	Functional Assessment of Cancer Therapy - Endometrial (FACT-EN)
<i>Cancer Generic</i>	European Organisation for the Research and Treatment of Cancer - Vulval (EORTC QLQ-VU34)
European Organisation for the Research and Treatment of Cancer - Cancer Generic (EORTC QLQ-C30)	Functional Assessment of Cancer Therapy - Vulval (FACT-V)
<i>Generic</i>	<i>Cancer Generic</i>
EuroQol-5 Dimensions-3 Level (EQ-5D-3L)	European Organisation for the Research and Treatment of Cancer - Cancer Generic (EORTC QLQ-C30)
State Trait Anxiety Index (STAI)	Functional Assessment of Cancer Therapy - General (FACT-G)
36-item Short Form health survey (SF-36)	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT-GOG/Ntx)
12-item Short Form health survey (SF-12)	<i>Generic</i>
Brief Pain Inventory (BPI)	EuroQol-5 Dimensions-3 Level (EQ-5D-3L)
Brief Fatigue Inventory (BFI)	36-item Short Form health survey (SF-36)
	12-item Short Form health survey (SF-12)
	Brief Pain Inventory (BPI)
	Female Sexual Function Index (FSFI)

As described in Project 2, individual summary cards detailing the key characteristics of each instrument were developed for each PROM measure. Such presented information included details on instrument acronym, area assessed and number of items, recall period, scoring information, estimated completion time, and copyright/licensing information. The summary cards for each PROM relevant to gynaecological cancers are included in Appendix VI (Tables 15-25). For reference, the summary cards developed by the IMI Prostate PIONEER Consortium as part of the synchronous localised and metastatic COSMIN systematic reviews are included within the Supplementary material of each publication (337, 338).

Alongside the summary card resources, an accompanying information pack was provided to all stakeholders involved in the decision-making process. This information pack was developed to include an explanation of each measurement property, as defined within the COSMIN guidelines, and instructions on how to interpret the results of each COSMIN assessment. Information related to the overall categorisation of each PROM measure and the accompanying recommendations, as defined in the Methods section of Project 2, were also provided to the stakeholders. Each PROM instrument appraised in the COSMIN assessment was categorised as below: (A) PROMs with evidence for sufficient content validity (any level) AND at least low-quality evidence for sufficient internal consistency which can be recommended for use and results can be trusted, (B) Have potential to be recommended but require further research, and (C) High quality evidence for an insufficient measurement property.

Additionally, information related to the availability of any translated versions of each instrument was collated for each PROM. Such information on translation availability was relevant for this site, as Guy's Cancer Centre serves an ethnically and socially diverse population. Details of any previous usage of each instrument within an NHS setting was also admissible to facilitate benchmarking and auditing at local and national levels. Data on the PROM instruments utilised in national surveys, such as the NHS Cancer Quality of Life Survey and the NHS England "Living with and beyond gynaecology cancers" pilot PROM collection commissioned in 2013, was also collated to provide further insight to the stakeholders.

In total, within the prostate clinical oncology setting specifically, ten clinical oncology consultant colleagues were involved in the PROM selection process. For the concurrent gynaecological PROM decision-making process, eight medical and clinical oncology specialist clinicians were engaged. The PROM tool selection process included an open dialogue to discuss the characteristics of each tool, including the results of each COSMIN assessment, and reach consensus on which instrument(s) to

select for collection at Guy's Cancer Centre specifically. The decision-making process and open discussions were facilitated by CM.

4.6.3 Results

4.6.3.1 Prostate oncology decision-making process

In summary, following an internal decision-making process within the prostate clinical oncology setting, stakeholders at Guy's Cancer Centre selected the Expanded Prostate Cancer Index Composite short-form 26-item version (EPIC-26) for collection in the radiotherapy prostate cancer population. EPIC-26 assesses domains related to urinary, bowel, sexual and hormonal functioning for prostate cancer patients during and after active treatment and can be completed by patients in 10-15 minutes. The tool has a recall period of four weeks and includes a license which enables free usage in hospital and academic settings. For reference, a specimen of the EPIC-26 questionnaire (adapted from the University of Michigan) is included in Appendix VII.

According to the PIONEER study on localised prostate cancer, EPIC demonstrated high internal consistency but low content validity and therefore was categorised as “(B) has the potential to be recommended but requires further research”. Content validity refers both to the relevance and comprehensiveness of the PROM instrument for the population of interest, as well as the comprehensibility of each item. In this PIONEER study, sufficient content validity was unable to be demonstrated owing to a lack of qualitative interview studies undertaken with localised prostate cancer patients. In the localised setting, the tool exhibited low structural validity but high internal consistency (summarised Cronbach's α 0.68-0.94) indicating that items within a subscale were well correlated and adequately measured the same construct (health-related quality of life). The reliability of EPIC was also moderate in the localised setting, demonstrated by summarised intraclass correlation coefficients of 0.08-0.88. Overall, EPIC-26 observed sufficient psychometric validity to allow its consideration for use in the localised prostate cancer setting, although further validation studies in prostate cancer populations are warranted.

In the second PIONEER led COSMIN assessment, which was undertaken in the metastatic prostate cancer setting, EPIC was not identified as a tool previously utilised in the randomised control trial setting for this patient cohort. Therefore, EPIC was not assessed according to COSMIN guidelines in the metastatic setting. Despite a lack of information on the validity and quality of the instrument in this setting, EPIC is a widely accepted across research and clinical settings as a well-established tool which has indications across disease stage and treatment modalities. For example, EPIC is administered to all stages of prostate cancer patients in the UK as part of the NHS National Prostate Cancer Audit (NPCA) in the 18-month period following initial diagnosis. This collection of the short-

form EPIC-26 version, which occurs as part of NHS benchmarking, also includes linkage of quality-of-life data with routine clinical information and disease characteristics.

When considering the collection of PROMs in the radiotherapy setting at Guy's Cancer Centre specifically, the stakeholders deemed the content of EPIC-26 sufficient to effectively assess the side effects of radiotherapy treatment. Multimodal radiotherapy and ADT treatment is often administered to prostate cancer patients with intermediate and high-risk localised disease following radical prostatectomy. As described in the ProtecT trial, bowel toxicity is the most commonly reported side effect of radiotherapy treatment, with symptoms manifesting as diarrhoea, bowel movement urgency, faecal incontinence and rectal bleeding (121). The EPIC-26 instrument includes an overarching subscale on bowel functioning which includes items assessing bowel movement urgency and frequency, faecal control, presence of blood in stools, and pain. Diarrhoea is a key side effect indicator of toxicity which is reported clinically both during and after radiotherapy treatment.

As previously described, ADT is commonly used in combination with radiotherapy treatment, and up to 93% of patients receiving ADT report sexual dysfunction (126). The EPIC-26 questionnaire assesses erection frequency and quality, as well as overall sexual functioning. In addition, EPIC-26 includes a subscale on hormonal functioning to appraise the side effects of ADT therapy. The hormonal functioning subscale comprises items relevant to assess hot flushes, depression, change in bodyweight, and low energy. Overall, the symptom burden of prostate cancer patients undergoing radiotherapy treatment is adequately assessed by the EPIC-26 instrument, and the short completion time of the PROM compared to similar measures ensures minimal burden to patients. Additionally, the tool has also been translated into more than seven languages which further provides the potential to administer across the diverse catchment population of Guy's Cancer Centre, without discrimination.

4.6.3.2 Gynaecology oncology decision-making process

Overall, the eight gynaecology oncology consultants reached consensus on alignment of instrument selection across the five gynaecological tumour types, and therefore opted for collection of the EORTC QLQ-C30 cancer core module with the addition of each cancer specific supplementary module, where available. For example, for cervical cancer patient populations, the EORTC QLQ-C30 and EORTC QLQ-CX24 instruments were selected for collection across oncology at this centre. For patients with womb cancer, the EORTC QLQ-C30 and EORTC QLQ-EN24 were chosen, and for ovarian cancer the EORTC QLQ-C30 and EORTC QLQ-OV28.

Each of the EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-EN24, and EORTC QLQ-OV28 questionnaires underwent critical appraisal according to the COSMIN guidelines as part of Project 2.

There existed one validation study assessing the psychometric properties of the EORTC QLQ-C30 in a population of gynaecological cancer patients. Overall, 140 gynaecological cancer patients were involved in this study and the COSMIN appraisal is therefore applicable across each of the five tumour types. The EORTC QLQ-C30 was classified as category (B) in this study indicating that the tool can be recommended for usage in the population of interest, but further study to assess the psychometric properties is required. Additionally, the EORTC QLQ-C30 is employed as part of the NHS Cancer Quality of Life Survey, which is a survey managed jointly by NHS England, and NHS Digital. This national initiative initially recruited breast, colorectal, and prostate cancer patients 18-months after the date of cancer diagnosis but expanded in July 2021 to incorporate gynaecological cancer patients. Latest figures, published in September 2022, indicate that, in total, 2352 gynaecological cancer patients have thus far completed the Cancer Quality of Life Survey (814 ovarian, 277 cervical, 1072 uterine, and 189 patients with other gynaecological malignancies) (391). Local alignment of Guy's Cancer Centre with national NHS initiatives was deemed integral to the decision-process, and therefore the EORTC cancer core module was selected for collection locally, along with the accompanying disease-specific gynaecological modules. Such alignment will, in turn, allow future comparative analyses between individual sites and the overarching national cancer population.

In total, three of the gynaecological specific EORTC supplementary modules were appraised according to the COSMIN guidelines and as part of Project 2. Overall, the EORTC QLQ-EN24 and EORTC QLQ-CX24 disease specific endometrial and cervical cancer modules were graded as category A, demonstrating that each exhibited adequate content validity and internal consistency when administered within their respective target populations. In contrast, the EORTC QLQ-OV28 was categorised as B, owing to insufficient evidence of internal consistency. Despite this insufficient grading, the EORTC QLQ-OV28 was able to be recommended for use in the population of interest, as six validation studies were identified for this tool in Project 2. Therefore, a large amount of evidence was available for each of the COSMIN graded measurement properties to support the use of this instrument in the routine clinical setting.

For each of the cervical, ovarian, and endometrial cancer types, only the European Organisation for the Research and Treatment of Cancer (EORTC) and Functional Assessment of Cancer Therapy (FACT) disease specific instruments were identified as applicable in each population. In contrast to the EORTC QLQ-CX24 instrument, the FACT-CX was categorised in group B, indicating that further studies to validate the tool psychometrically are warranted. Indeed, only two validation studies were identified for this tool, compared to eight for the EORTC QLQ-CX24. The FACT-CX tool exhibited insufficient internal consistency and there was a lack of available evidence for various of the other

measurement properties. For endometrial cancer, only the EORTC QLQ-EN24 underwent appraisal according to COSMIN guidelines. The FACT-EN endometrial module was not taken forward for inclusion in Project 2, owing to its application in one study alone, as identified in Project 1 of this Chapter. Indeed, when a subsequent independent literature search was conducted for FACT-EN specifically, there existed a lack of published validation studies of the module in endometrial populations. The available evidence from Project 2 therefore lent itself to selection of the EORTC QLQ-C30 and gynaecology specific submodules, despite the EORTC QLQ-OV28 instrument being graded lower than its FACT-O counterpart.

As well as the availability of more psychometric evidence to support the implementation of the EORTC core and supplementary modules, the EORTC QLQ-C30, EORTC QLQ-CX24, EORTC QLQ-OV28, and EORTC QLQ-EN24 were employed as part of a commissioned NHS pilot PROMs survey in 2013. This pilot study recruited patients with cervical, ovarian, and uterine cancer, and a gynaecological cancer generic tool formed of 106 items was developed from these existing instruments. In total, 1832 women responded to the survey 1-5 years following their initial treatment for cervical, ovarian, or uterine cancer, translating into response rates of 55% for ovarian cancer, 39% for cervical cancer, and 52% for uterine cancer. The questionnaire was administered across treatment modalities. Such pilot study provided a further rationale to select the EORTC modules, to enable alignment with the various NHS initiatives occurring at a national scale.

For vaginal and vulval cancer patients, no disease-specific PROM instruments were identified in Project 1 as having been applied previously in each population. As such, no tool underwent quality assessment according to COSMIN guidelines. Further research identified, however, that an EORTC vulval cancer specific module (EORTC QLQ-VU34) is currently in Phase IV of development undergoing formal field testing with psychometric analyses. Additionally, a FACT-V vulval module has previously been developed, although its use across research and the clinical setting appears limited. To ensure alignment across the five gynaecological tumour types, the stakeholders involved in the local decision-making process agreed to commence collection of the EORTC QLQ-VU34 vulval cancer module with the accompanying EORTC QLQ-C30 generic module once formal validation is complete.

Owing to the low incidence of vaginal cancer worldwide, to date there have been no disease-specific PROM instruments developed for application in this population. Common side effects of vaginal cancer and associated treatments include sexual dysfunction, urinary incontinence, and bowel dysfunction. Sexual dysfunction manifests through radiotherapy-associated shortening of the vaginal canal, and vaginal dryness, as well as numbness, loss of sexual pleasure, dyspareunia, and fibrosis. Common bowel related symptoms after radiotherapy include defecatory urgency and faecal

incontinence, and loose stools and diarrhoea. Cervical cancer patients undergoing radiation and surgical treatment report similar side effects and symptoms to vaginal cancer patients, particularly related to sexual dysfunction. Indeed, many cervical cancer patients suffer issues related to orgasm functioning, vaginal shortening, dyspareunia, genital numbness, and sexual dissatisfaction. Additionally, cervical cancer patients experience similar urinary and bowel dysfunction to those symptoms reported by vaginal cancer populations. As such, stakeholders involved in the gynaecology oncology consensus process at Guy's Cancer Centre recommended that the EORTC QLQ-CX24 cervical cancer module could be repurposed for use in vaginal cancer populations. This supplementary module was again selected to be administered in accompaniment to the EORTC QLQ-C30.

4.6.4 Conclusions

In summary, two local shared decision-making processes were undertaken concurrently in the prostate and gynaecology oncology settings of Guy's Cancer Centre. Following an in-depth appraisal of information, incorporating the results of the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) assessments (Project 2 and the IMI PIONEER Consortium), PROM instruments were selected for routine clinical collection in each setting. Stakeholders involved in the decision-making process were equipped with information packs to facilitate comprehension of the COSMIN assessment process and results, and key instrument characteristics such as average completion time, licensing information, and previous use in local and national settings were also presented.

Overall, in the prostate clinical oncology setting of Guy's Cancer Centre, the clinical oncology consultant body selected the Expanded Prostate cancer Index Composite short-form version (EPIC-26) for completion prior to, during, and following completion of radiotherapy treatment.

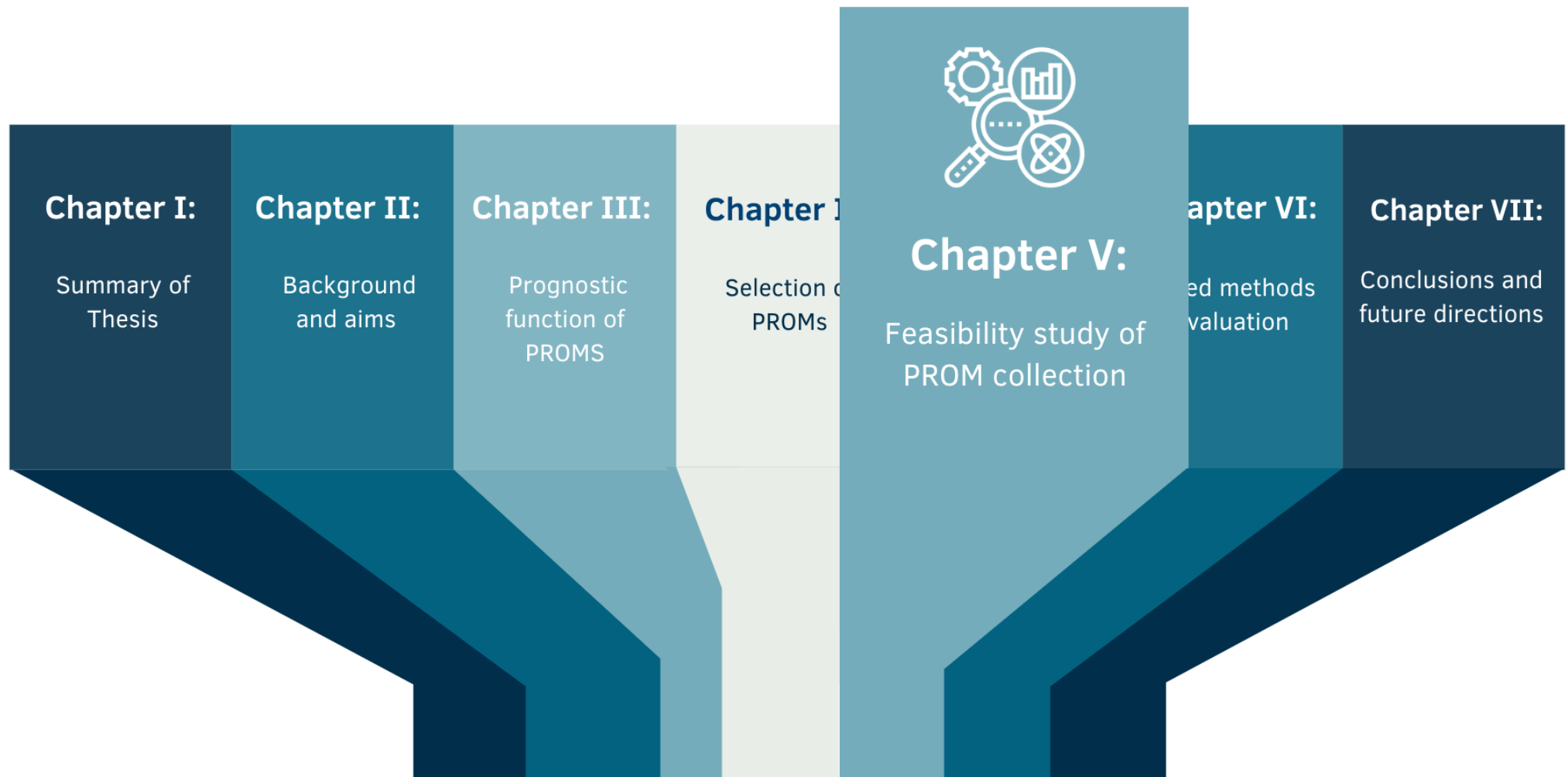
In the gynaecology oncology setting, clinical and medical oncology consultants opted for routine clinical collection of the European Organisation for the Research and Treatment of Cancer (EORTC) cancer core module (EORTC QLQ-C30) and relevant gynaecology submodules. Therefore, the EORTC QLQ-C30 and EORTC QLQ-CX24 instruments were selected for collection in the local cervical cancer population of Guy's Cancer Centre. For endometrial and ovarian cancer, the EORTC QLQ-C30 was chosen for adoption with the EORTC QLQ-EN24 and EORTC QLQ-OV28 disease-specific modules, respectively. Currently, the EORTC vulval cancer module is under Phase IV of development but the Guy's Cancer Centre stakeholders agreed to commence collection of this module with the EORTC QLQ-C30 core questionnaire once validated. Finally, no vaginal cancer specific PROM instruments exist in the literature. Therefore, in view of the similarities in disease and treatment side effects

between vaginal and cervical cancers, the stakeholders agreed to implement collection of the EORTC cervical cancer module, EORTC QLQ-CX24, as this tool adequately assesses such side effects and symptoms in this patient cohort.

Chapter V:

Feasibility study of PROM collection

This chapter refers to a feasibility study of routine clinical PROM collection which was designed and conducted within the prostate radiotherapy setting of Guy's Cancer Centre. Brief outcomes related to the effectiveness of routine PROM collection are included.



5. Chapter V: Feasibility study of routine clinical PROM collection at Guy's Cancer Centre

Thus far, this thesis has worked to present a clear rationale to support the routine collection of PROMs within cancer healthcare settings. Briefly, PROMs can be utilised to identify patient concerns, enhance patient-clinician communication, and improve patient satisfaction with care in the clinical setting (20, 21). Importantly, Chapter III also presented an alternate justification for the routine clinical collection of PROMs, describing how questionnaires collated at baseline and follow-up timepoints acted as independent prognosticators for oncological outcomes (392).

Moreover, Chapter IV outlined a three-step process designed to select highly valid, reliable, and sensitive PROMs for application in the routine clinical setting of Guy's Cancer Centre. This work addressed an important barrier impacting the routine clinical collection of PROMs, in terms of the selection of the most appropriate tool(s) for collection in the population(s) of interest.

Despite established rationale to support routine clinical PROM collection, to date, no implementation attempt has been undertaken in the cancer clinical setting of Guy's Cancer Centre. Therefore, the following Chapter of this thesis describes a feasibility study of routine clinical PROM collection which was developed as the first exploratory attempt to implement routine PROM collection at this site. The feasibility study was conducted in the prostate radiotherapy treatment setting and mixed method process evaluation was embedded to identify key barriers and enablers impacting implementation success. The development of the feasibility study was informed by the Medical Research Council (MRC) guidance for complex interventions. Overall, this feasibility study aimed to elucidate the key components requiring consideration when implementing PROMs, and initiate the development of strategies, or recommendations, to address identified barriers.

Patient recruitment was limited to the prostate radiotherapy setting as this feasibility study represented the first exploratory attempt to implement PROMs at Guy's Cancer Centre. It was anticipated that scale-up of the feasibility study, including broadening of the inclusion criteria to recruit gynaecological cancer patients, could occur once key implementation barriers had been identified and addressed. This thesis aimed to identify components requiring consideration when implementing routine clinical PROM collection at Guy's Cancer Centre, and therefore it was presumed that implementation strategies identified during this feasibility study would be generalisable and applicable across various tumour settings.

Chapter V presents the planning and design elements of this feasibility study and reports data around patient outcomes and the effectiveness of the intervention. As described, the feasibility study was developed in line with the MRC guidance for complex interventions and a background for this framework is provided below for reference. Additionally, detailed background on the discipline of implementation science as well as the Consolidated Framework for Implementation Research (CFIR) is provided. The CFIR was selected to provide a theoretical basis for approaching the implementation of routine clinical PROM collection at Guy's Cancer Centre.

Chapter VI subsequently presents observation-based, and qualitative and quantitative evaluative data on the key barriers and enablers which were identified as impacting the success of this feasibility study. The CFIR was employed to guide data collection, coding, analysis, and reporting of findings, and to support a comprehensive understanding of identified barriers and enablers. Following this, the Expert Recommendations for Implementing Change (CFIR-ERIC) compilation was utilised to develop actionable findings to improve the effectiveness of implementation, and to identify potential improvements to implementation strategies for future real-world collection of PROMs at Guy's Cancer Centre. The CFIR-ERIC compilation maps to the constructs of the CFIR and seeks to guide selection of implementation strategies based on the results of a context assessment. A brief overview of the CFIR-ERIC compilation is included below within the background section of the CFIR (Section 5.1.2).

5.1 Background

5.1.1 Implementation Science

Implementation science is an emerging discipline within the field of health research which seeks to promote the systemic uptake of evidence-based practice into routine practice, thereby improving the quality and effectiveness of health services (393). Implementation research incorporates all aspects of implementation; from the identification of factors which affect implementation, to understanding the processes which underpin implementation, and development and introduction of potential solutions which enable the scale-up and sustainability of implementation (393). The overall intent of implementation science involves garnering an understanding of what, why, and how interventions work in real-world settings, and testing novel improvement approaches.

Over recent years, a growing number of implementation frameworks have been developed to both provide a theoretical basis for approaching implementation, and to guide researchers from early feasibility testing through to longer term sustainability. These implementation frameworks range from process theories, which are used to guide the process of translating research into practice, to

determinant frameworks, which describe factors that influence implementation outcomes, and evaluation frameworks which provide a structure for evaluating implementation endeavours.

For the purposes of this thesis, a determinant framework was employed to guide the process of identifying key barriers and enablers, or contextual factors, influencing the implementation of routine clinical PROM collection at Guy's Cancer Centre. Specifically, the Consolidated Framework for Implementation Research (CFIR) was selected as a highly cited tool which aims to predict and/or explain the barriers and enablers to implementation effectiveness, and to inform the selection of implementation strategies to overcome these (394, 395).

5.1.2 The Consolidated Framework for Implementation Research

Current literature estimates that up to two thirds of evidence-based interventions fail to successfully translate into meaningful outcomes across the healthcare landscape (396). Barriers impeding successful translation can occur at multiple levels of the implementation process, including the patient and/or provider level, the organisation level, and the policy level. It is therefore pertinent to perform process evaluation alongside evaluation of outcome endpoints, to optimise the benefits of the intervention, assess outcomes related to implementation, and promote scale-up and sustainability in real-world settings.

The CFIR was established by Damschroder et al in 2009 with the aim of aligning the differing terminologies and definitions existing throughout the various alternate implementation theories (397). Overall, the CFIR consists of an overarching list of selectable constructs which promote theory development and verify what works where, and why, across multiple contexts.

The CFIR comprises five domains (the intervention, the inner and outer setting, the individuals involved, and the process by which the implementation is accomplished) which interact to influence the effectiveness of implementation. The first domain relates to the characteristics of the intervention being implemented in a particular organisation and necessitates the alignment and engagement of key stakeholders, as well as the adaptation of the intervention for a particular setting. The routine clinical collection of PROMs is a complex and multi-faceted intervention. This intervention can be conceptualised as having core essential components and an adaptable periphery (adaptable features relevant for the setting in which it is being implemented). For example, a core component of this intervention is the collection of PROMs at clinically relevant timepoints, and an adaptable periphery of the intervention is the electronic platform utilised to collect the questionnaires.

The second and third domains of the CFIR are the inner and outer settings. Usually, the outer setting incorporates the economic, political, and social context within which the organisation is located, and the inner setting includes the structural, political, and cultural contexts through which the intervention will proceed.

The fourth domain of the CFIR concerns the individuals involved in the intervention and the process of implementation. Finally, the fifth domain of the CFIR is the implementation itself. This domain incorporates the four other domains of the CFIR; whereby an active change process is required to facilitate successful implementation and achieve individual and organisational level use of the intervention as planned. Equally, individuals from the inner and outer setting may actively promote the implementation process.

Overall, the CFIR comprises five interrelated domains which support the identification and exploration of determinants which may be identified during an implementation process. This framework was selected for use in this thesis to provide the necessary theoretical basis to assess the process of implementation of the proposed routine clinical PROM collection programme at Guy's Cancer Centre. This programme is categorised as a complex intervention, and to improve the likelihood of successful implementation, guidance from the Medical Research Council was employed to develop an observational feasibility study at Guy's Cancer Centre prior to full implementation. The feasibility study was developed to permit small-scale, real-world testing and identify barriers and enablers to facilitate a smoother implementation process at this site in the longer term. Mixed methods evaluation, developed using the CFIR, was undertaken to facilitate improvements to the implementation using tailored implementation strategies. Such implementation strategy development was guided by the Expert Recommendations for Implementing Change (CFIR-ERIC) compilation:

5.1.2.1 Expert Recommendations for Implementing Change (CFIR-ERIC)

In recent years, research focusing on implementation strategies, which are defined as “methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program or practice” has been prioritised for the purposes of providing contextual clarity and standardising terminology (398). Various taxonomies of implementation strategies have previously been developed, but are noted to be purposely narrow in scope in terms of their fields of practice and/or target consumers (399). Therefore, the CFIR-ERIC project sought to pursue opportunities for implementation improvement, and a modified Delphi process was undertaken to compile 73 discrete implementation strategies, applicable across a range of implementation contexts (400). This work was undertaken primarily to standardise definitions and terminology, and the resulting CFIR-

ERIC compilation is applicable across a wide range of settings (395). The implementation strategies of CFIR-ERIC map against the five constructs of the CFIR to permit selection of implementation strategies to address specific identified barriers. These 73 implementation strategies were used to guide the development of implementation strategies to overcome the barriers locally at Guy's Cancer Centre.

This qualitative and quantitative evaluation is included separately within Chapter VI. A brief background of the Medical Research Council Framework for Complex Interventions is provided below, for reference.

5.1.1 Medical Research Council Framework for Complex Interventions

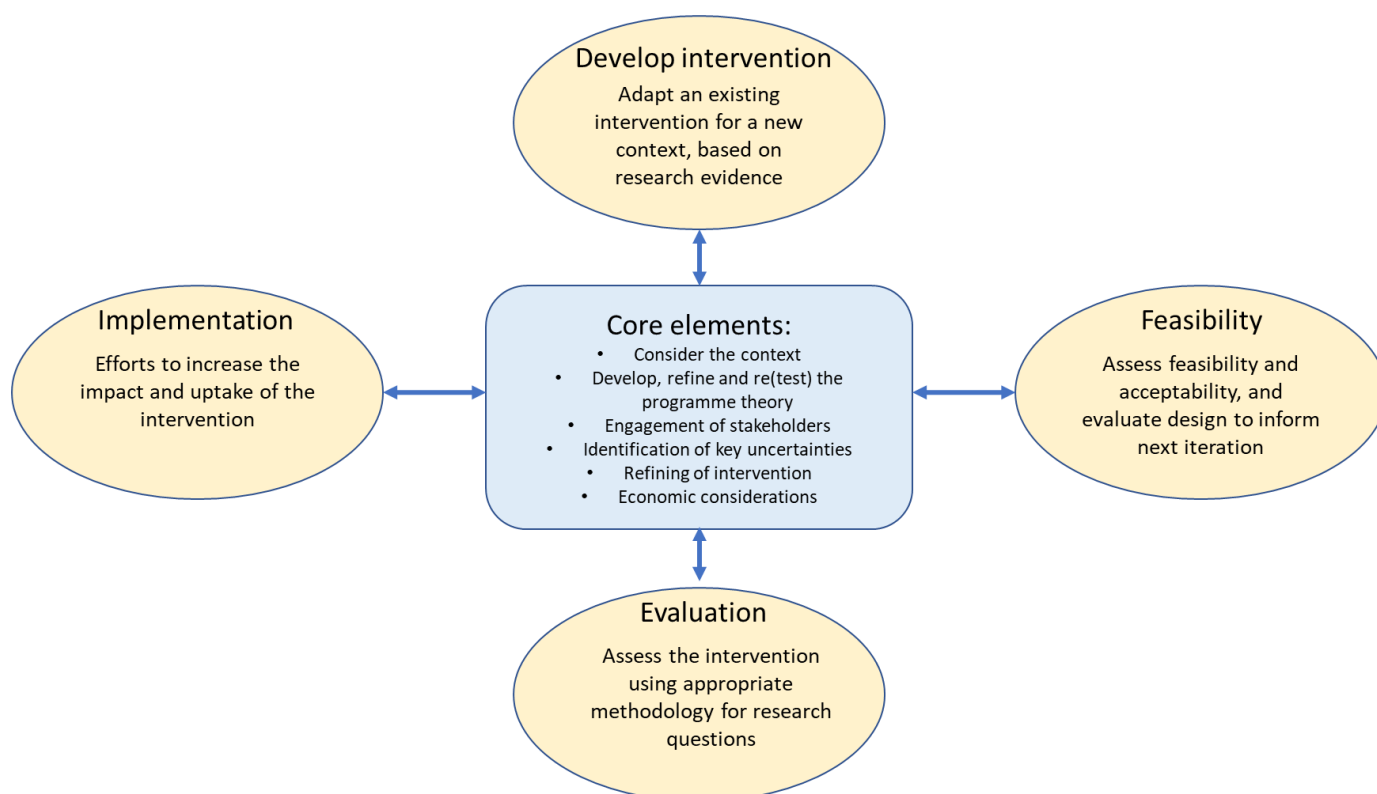
According to the Medical Research Council (MRC) Framework for Complex Interventions, the implementation of routine clinical PROM collection is defined as a complex intervention owing to the involvement of multiple interacting components and non-linear causal pathways (401). Guidelines initially published by the MRC in the year 2006 provide further detail on the definition of a complex intervention stating that “complexity resides in the number of interacting components; the number and difficulty of behaviours required by those delivering or receiving the intervention; the number of groups or organisational levels targeted by the intervention; the number and variability of outcomes; and the degree of flexibility or tailoring of the intervention permitted” (402). Complex interventions span the healthcare landscape with some examples including interventions which promote community-based health, pay for performance interventions to improve health service quality, and strategies for implementing clinical guidelines (403).

Previous iterations of the MRC complex intervention framework were developed principally to address the question of whether an intervention was effective. Updated guidance, published in 2021, acknowledged, however, that this primary focus had led to failures in the delivery of interventions which are implementable, cost-effective, transferable, and scalable in real-world conditions (404). As such, the previous guidance was amended to stipulate the necessity of strong and early engagement with key stakeholders (including patients, practitioners, and policy makers) to facilitate the shift in focus from assessing effectiveness to assessing whether the intervention is acceptable and implementable.

The MRC framework involves four phases of complex intervention research including development or identification of the intervention, feasibility and piloting, evaluation, and implementation. The guidance dictates that a research programme may commence at any phase dependent on uncertainties arising about the planned intervention. Each of the four phases share a common set of core elements which should be continually revisited throughout the research process. The four

phases of complex intervention research, including the core elements relevant for each phase, are presented in Figure 6. The core elements for consideration in each phase of complex intervention research are outlined in detail below, following more detailed definitions of each phase.

6. Figure 6: Summary of the MRC Framework for delivering complex interventions, including the four phases of complex intervention research and the core elements underpinning each phase. Figure adapted from the updated 2021 guidance (404).



5.1.1.1 Phases of complex intervention research

Developing or identifying a complex intervention

The development phase describes the whole process of designing a complex intervention, and encompasses the initial conception of an intervention, through to feasibility, pilot, and evaluation. In the context of the proposed programme of routine clinical collection of PROMs at Guy's Cancer Centre, the intervention is well defined in the randomised control setting but is yet to be adapted to the context of an NHS routine setting.

Feasibility

The value of feasibility testing has previously been overlooked when implementing interventions, however this process forms a critical step in appraising various factors including recruitment, retention, outcomes, acceptability, and capacity. Refinement of the key uncertainties identified

during the development and feasibility phases can facilitate the success of full implementation. Chapter V of this thesis is based on a feasibility study which was developed and conducted in the prostate radiotherapy setting of Guy's Cancer Centre.

Evaluation

There are multiple dimensions of evaluation which transcend assessment of effectiveness alone. Broadly, evaluation includes questions related to the impact of the intervention, development of theory around how the intervention works, and how the intervention interacts in the context in which it is implemented. Evaluation also includes assessment of how an intervention contributes to a system change, and how evidence generated can be utilised to support decision making in real-world settings. A mixed methods approach, incorporating qualitative analyses alongside process evaluation, is often a requisite for the evaluation process. Process evaluation can be employed to investigate the fidelity and quality of an implementation and can occur simultaneously with outcome evaluations such as feasibility trials. In the context of this thesis, mixed methods evaluation of the feasibility study was employed to explore uncertainties and optimise the implementation of PROMs in routine clinical settings. Qualitative and quantitative evaluation was embedded within the feasibility study, and the findings of these analyses are reported within Chapter VI.

Implementation

Early consideration of implementation is warranted to maximise the potential of developing a complex intervention which is widely adoptable and can be scaled up in real-world settings. Questions around implementation should be considered throughout each phase of complex intervention research, including assessment of the contextual factors that facilitate or impede the programme.

5.1.1.2 Core elements underpinning each phase of complex interventions

How does the intervention interact with its context?

The efficacy of a complex intervention is impacted by the context, or setting, in which it is implemented – an intervention which is effective in one setting may be harmful in another, and interventions can modify the context in which they are implemented in (405). Context is considered dynamic and multi-dimensional, and key dimensions include organisational, spatial, or political features of healthcare.

What is the underpinning programme theory?

Programme theory is a model which refers to the interaction between the key components of the intervention, including the expected elicited effect and the impact of the context (406). Programme theory can be employed to facilitate the shared understanding of the intervention across stakeholders, and to identify key uncertainties arising.

How can diverse stakeholders' perspectives be included in the research?

Stakeholders are defined as any individual targeted by the intervention, persons involved in the development or delivery of the intervention, those with a professional or personal stake in the intervention, and patients/the public (407). Meaningful engagement with stakeholders is required to maximise the potential of developing an impactful intervention.

What are the main uncertainties?

There are many questions which can be answered during each phase of complex intervention research, and the design and conduct of the research process should work to explore and prioritise these identified uncertainties (408).

How can the intervention be refined?

The complex intervention is required to be refined as it transitions through each research phase (409). Refinement can occur based on data collected and/or further development of programme theory and can lead to improvements in intervention feasibility and acceptability through engagement of potential users.

Do the effects of the intervention justify its costs?

A comparative economic evaluation of alternate courses of action, specifically regarding costs and outcomes, should be completed for each phase of intervention research to identify the full range of benefits of the intervention (410).

5.3 Methods

As described in the MRC framework for complex interventions, feasibility testing is now widely accepted as a valuable phase of developing and evaluating complex interventions (404). When considering the routine clinical collection of PROMs at Guy's Cancer Centre, the described feasibility study was developed to assess various uncertainties related to implementation success and outcomes, including, but not limited to, optimisation of delivery, acceptability, adherence, and capacity. These uncertainties were evaluated using mixed qualitative and quantitative methods

which were embedded within the feasibility study itself. The results of the evaluation and description of emerging implementation strategies are presented separately, in Chapter VI of this thesis.

5.3.1 Feasibility study development

5.3.1.1 Ethical clearance

As it is anticipated that the collection of PROMs will become integrated within routine standard of care, ethical clearance was not required to develop and undertake this feasibility study. Within the feasibility study, PROMs were integrated as part of standard of care for a consecutive population of prostate cancer patients undergoing radiotherapy treatment for their disease.

5.3.1.2 Radiotherapy working group

Although ethical approval was not necessitated for this feasibility study, the proposed implementation was presented to the Radiotherapy Operating Group (ROG) of Guy's and St Thomas' NHS Foundation Trust. The ROG is formed of clinicians, radiographers (therapy radiographers and advanced practice radiographers), clinical nurse specialists, dosimetrists, and support staff (comprising management and administrative positions), all of which are roles deemed as key stakeholders in this implementation process. The implementation was proposed to the ROG and the group worked collaboratively to define some of the main features of the feasibility study, including:

1. Defining the number of patients required to be recruited to this small-scale feasibility study.
2. Proposing the intervals between PROM administration, being cognizant of current clinical scheduling.
3. Describing the software requirements for collecting PROM questionnaires electronically.
4. Appraising item and subscale domain scores for the PROM instrument and defining how these scores would translate into clinical management.

Once the features of the implementation process to be tested had been agreed with the stakeholders, the feasibility study was provided sign off by the ROG at a meeting held on the 16th of June 2021.

5.3.1.3 Feasibility study population

A consecutive population of men with prostate cancer who had been referred for radiotherapy treatment were recruited at Guy's and St Thomas' NHS Foundation Trust (August 2021-March 2022). The men were approached in the clinical setting prior to commencement of radiotherapy and were asked to complete PROMs at predefined timepoints prior to, and following completion of, treatment. The men were recruited at Guy's Cancer Centre and Queen Mary Hospital, which is

located in Sidcup, London. Queen Mary Hospital is a satellite site of Guy's and St Thomas' NHS Foundation Trust which provides radiotherapy treatment to Guy's Cancer patients. The location of this radiotherapy site allows cancer patients from the wider catchment area of Guy's Cancer Centre to attend radiotherapy treatment in a location which is closer to their home. As this study was developed as a small-scale feasibility study, no power calculation was warranted. Overall, 20 consecutive prostate cancer patients were recruited, and this number was deemed sufficient to facilitate the identification of a comprehensive list of barriers and enablers impacting implementation.

5.3.1.4 Use of the EPIC-26 PROM

As outlined in Project 3 of Chapter IV, a local consensus process undertaken in the prostate radiotherapy setting of Guy's Cancer Centre selected the Expanded Prostate Cancer Index Composite short-form (EPIC-26) instrument for routine clinical collection.

Briefly, the EPIC-26 tool is the 26-item short form version EPIC which was developed jointly at the University of Michigan and the University of California to assess health-related quality of life across five prostate cancer specific domains (411). For reference, the full version of the EPIC-26 questionnaire is included in Appendix VII. EPIC and its short form EPIC-26 version have been widely utilised across research and clinical settings, including as part of the NHS National Prostate Cancer Audit where the EPIC-26 questionnaire is administered 18 months post prostate cancer diagnosis.

The EPIC-26 questionnaire consists of 26 items which are categorised into five overarching subdomains comprising urinary incontinence, urinary irritation, bowel functioning, sexual functioning, and hormonal functioning. Response options for each item of the EPIC-26 tool form a Likert scale, and multi-item scale scores are transformed linearly to a 0-100 scale. Overall, a higher score per domain represents a better health-related quality of life.

5.3.1.5 Scoring of the EPIC-26 PROM

According to the Scoring Instructions for the EPIC-26 manual, scoring the questionnaire involves two steps. Step 1 entails standardisation of each item; each Likert scale value is transformed to a value on a scale of 0-100. Table 24 outlines each question number, the accompanying item Likert response value for each question, and the standardised value for transformation of each question.

Table 24: Standardisation of the response for each item of the EPIC-26 questionnaire, by question number. Adapted from the Scoring Instructions for the Expanded Prostate cancer Index Composite manual included online: Scoring Instructions for the (umich.edu)

Question number (EPIC-26 questionnaire)	Item response value	Standardised value
1, 8a, 8b, 10, 11	1	0
	2	25
	3	50
	4	75
	5	100
2, 9	1	0
	2	33
	3	67
	4	100
3	0	100
	1	67
	2	33
	3	0
4a, 4b, 4c, 4d, 4e, 6a, 6b, 6c, 6d, 6e, 13a, 13b, 13c, 13d, 13e	0	100
	1	75
	2	50
	3	25
	4	0
5, 7, 12	1	100
	2	75
	3	50
	4	25
	5	0

Following transformation of the Likert responses per question item, the second step of scoring involves calculation of an average standardised value per subscale to create a summary score for each of the health-related quality of life domains. Table 25 outlines which question items are included within each of the five domains of EPIC-26 and reports a restriction on computation of a score if some item responses are missing. The general rule when calculating a domain summary score or subscale score is that if 20% of the items within the domain are missing, the summary score cannot be computed.

Table 25: Calculating the summary scores for each domain of the EPIC-26 questionnaire. An average score is computed using the standardised 0-100 scores assigned per question item. Table 24 outlines the question items included in each domain and notes the number of items required to be non-missing to calculate.

HRQoL Domain Summary Scores	Question items comprising the domain (average of these items calculated)	Number of non-missing items required to calculate score
<i>Urinary Incontinence</i>	1, 2, 3, 4a	4
<i>Urinary Irritation</i>	4b, 4c, 4d, 4e	4
<i>Bowel Functioning</i>	6a, 6b, 6c, 6d, 6e, 7	5
<i>Sexual Functioning</i>	8a, 8b, 9, 10, 11, 12	5
<i>Hormonal Functioning</i>	13a, 13b, 13c, 13d, 13e	4

Alongside the online Scoring Instructions manual, the University of Michigan has published minimally important differences (MIDs) for the EPIC-26 questionnaire. MIDs are defined in the literature as the smallest measurable change in the outcome score that will make a difference to the patient (412). Skolarus et al utilised two approaches, including distribution-based and anchor-based methodology, to calculate these MIDs for the five domains of the EPIC-26 questionnaire (413). This study involved utilising a longitudinal cohort of 1021 prostate cancer patients with stage 2 or 3 disease who received primary treatment of radical prostatectomy, brachytherapy, or external beam radiotherapy. EPIC-26 questionnaire data collated at pre-treatment and 1-year, 2-year, and 3-year post-treatment timepoints was utilised.

The distribution-based approach involved comparing changes in the EPIC-26 scores with corresponding standard deviations (SD) for each domain. Previous literature dictates that one-third of and one-half of an SD are appropriate for distribution-based cut-offs; with one-half of an SD representing a medium-sized effect and one-third of an SD representing a small effect. In this study, the mean and SD of the EPIC-26 values for each domain were calculated at each timepoint, and were further used to determine the one-half and one-third SD values and corresponding MID values.

Conversely, an anchor-based approach was utilised to examine within-patient and between-patient EPIC-26 scores corresponding to an external criterion. Generally, anchor-based approaches are employed to compare PROM scores with another subjective assessment to detect MIDs. Within this study, an anchor-item was chosen from the Service Satisfaction Scale for Cancer Care (SCA) scale. Statistically, both unadjusted and age-adjusted linear regression was used to model changes in EPIC-26 domain scores from pre-treatment to 1-year, 2-year and 3-year follow-up. The changes in model-adjusted scores were calculated between adjacent anchor-item levels. Both approaches were used to generate the minimally important differences per EPIC-26 domain. Collated data was used to

inform recommended ranges for clinically meaningful differences in EPIC-26 scores for each domain. These MID ranges are outlined, per health-related quality of life domain, in Table 26.

Table 26: Minimally Important Differences (MIDs) for EPIC-26, as calculated by Skolarus et al using a longitudinal sample of prostate cancer patients (413). Two approaches were employed to determine the MIDs, and averages were pooled between these methodologies. Each MID represents a clinically meaningful difference in EPIC-26 scores across each timepoint.

EPIC-26 Domain	Minimally Important Difference (change in EPIC-26)
<i>Urinary incontinence</i>	<i>6-9 points</i>
<i>Urinary irritation</i>	<i>5-7 points</i>
<i>Bowel functioning</i>	<i>4-6 points</i>
<i>Sexual functioning</i>	<i>10-12 points</i>
<i>Hormonal functioning</i>	<i>4-6 points</i>

As part of this feasibility study, the described minimally important differences were utilised to guide interpretation of the PROM scores in the routine clinical setting. Some limitations in these thresholds were identified at the outset, however, including concerns around the generalisability of these MIDs to the cohort of prostate cancer patients undergoing radiotherapy at this site, specifically.

The use of the MIDs relies on an average score being calculated per domain of health-related quality of life. When designing the feasibility study, concerns were raised around patient compliance and completion of the EPIC-26 instrument, especially with regard to some of the sensitive items included in the sexual functioning domain. It is not possible to employ the MIDs in domains where some data items are missing. With this in mind, the raw scores for each question were also presented to clinicians to allow identification of specific items which may be impacting the overall domain score, and in cases where missing data was an issue. For example, the hormonal functioning domain encompasses items related to hot flashes, breast tenderness, depression, levels of energy, and bodyweight. Raw scores for each item were presented to allow the clinical teams to identify whether specific symptoms of each overarching domain were impacting patient quality of life. This would then facilitate tailored follow-up care, personalised to that patient's specific symptom burden.

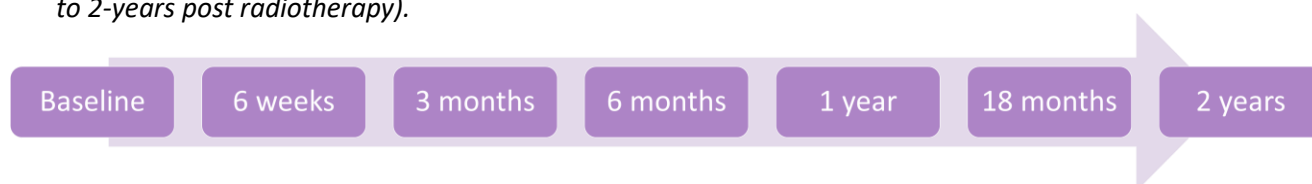
5.3.1.6 Timepoints for EPIC-26 administration

A key objective of the proposed feasibility study was elucidation of an optimal follow-up schedule for PROM administration, whilst remaining cognizant of clinical follow-up assessments as well as patient and healthcare professional burden. A follow-up schedule was developed for the purposes of this feasibility study, and outcomes related to alignment with clinical monitoring pathways, patient

acceptability and compliance, and service-provider burden were evaluated to assess the longer-term suitability and sustainability of such schedule.

The schedule of PROM administration which was assessed within this feasibility study is outlined below in Figure 7. Briefly, the baseline EPIC-26 questionnaire was administered following patient attendance at a pre-treatment appointment where consent is sought for the patient to receive radiotherapy. Following this, follow-up questionnaires were administered at six further timepoints calculated using an end of radiotherapy treatment date. The follow-up timepoints were selected based on the local schedule of clinical review following completion of radiotherapy. Prostate cancer patients treated at Guy's Cancer Centre are reviewed both in consultant-led clinics and as part of a radiographer-led clinics at various timepoints following radiotherapy treatment. The follow-up timepoints of 6-weeks, 3-months, 6-months, 1-year, 18-months, and 2-years were therefore selected to align with these follow-up appointments, and to facilitate healthcare provider review of patient symptom burden as highlighted by the EPIC-26 questionnaire.

7. Figure 7: Proposed schedule of EPIC-26 completion for prostate cancer patients at Guy's Cancer Centre, at Baseline (pre-radiotherapy) and following completion of radiotherapy treatment (6-weeks to 2-years post radiotherapy).



5.3.1.7 Stakeholder involvement

The stakeholders involved in the design phase of this feasibility study also held key roles in facilitating the implementation pilot. The feasibility study was undertaken with input from local advanced practice radiographers who acted primarily as a point of liaison for the prostate cancer patients. The advanced practice radiographers were tasked with recruitment to the feasibility study; consecutive prostate cancer patients were approached in the clinical setting and provided with relevant information related to the implementation pilot. Patients were also counselled by the radiographers on the content of the EPIC-26 questionnaire and the potential impact of routine clinical PROM collection on their clinical management and care standards.

Two modes of administration were offered to the patients within the feasibility study; patients could either opt for electronic PROM collection or pen and paper completion. Both modes were offered to enable assessment of the feasibility and acceptability of the differing methods, and to evaluate the impact of each on implementation success and sustainability. Patients who opted for pen and paper completion of the EPIC-26 were posted the questionnaires at the relevant follow-up timepoints. The posted questionnaires were returned directly to the radiographer department to enable entering of

the responses onto the electronic platform housing the study. Patients who opted to complete the EPIC-26 PROM electronically received the follow-up questionnaires directly from the study platform, according to the follow-up schedule.

Following the initial recruitment of patients onto the feasibility study, I worked with the radiographers to monitor patient compliance levels related to the follow-up schedule of EPIC-26 completion. A schedule of two reminders per patient was agreed for each timepoint during the design stage of the feasibility study, and radiographer colleagues adhered to this by performing reminder phone calls or approaching non-compliant patients in the clinical setting.

The radiographers also performed high-level review of the scores of the EPIC-26 questionnaires to identify patients potentially requiring further clinical management or intervention. During the planning phase, it was anticipated that the radiographers could flag patients with more severe symptom burden requiring further clinical management to the clinical oncologists.

5.3.1.8 Electronic infrastructure

A key component of the feasibility study involved selection of an appropriate multifunctional electronic platform which could be employed to collect, store, and report the collated data. Within the scope of this exploratory implementation study, there were two platforms which were identified as potentially fit for purpose – namely REDCap and DrDoctor. During the planning phase of this feasibility study, I undertook critical appraisal of these platforms and presented the differing functionalities, as well as the pros and cons of each to the Radiotherapy Operating Group. Based on this information, a collective decision was taken to use REDCap for the purposes of this feasibility study. The rationale behind this decision is outlined below in each platform's section however, briefly, REDCap includes automated survey invitation functionality, as well as internal reporting and clinical interoperability features.

5.3.1.8.1 DrDoctor

DrDoctor is a booking and patient interaction software which was first developed in London in 2012 (414). Guy's and St Thomas' NHS Foundation Trust first commenced use of DrDoctor in 2018, in an effort to reduce the effects of "did not attend" appointments and better manage waiting list times. Essentially, the DrDoctor platform sits above an appointment management solution which allows patients to amend, cancel or rebook their clinical appointments using their smart phones.

Alongside patient-led booking functionality, the DrDoctor platform also includes an assessment feature where questionnaires and forms can be sent directly via text message to the patient. An invitation access link is included within this text, and messages are triggered based on outpatient

clinic codes i.e., if a patient is scheduled to attend an appointment at a specific outpatient clinic, a form is triggered based on this appointment invitation. For the purposes of this feasibility study, the REDCap platform was selected over DrDoctor owing to the required creation of novel clinic codes to trigger sending of the EPIC-26 PROM at the defined follow-up timepoints within DrDoctor. In contrast, a tailored follow-up schedule could be designed on REDCap without use of clinic codes.

Additionally, appraisal of both platforms identified that the DrDoctor platform does not include the same specification of data management as is possible within REDCap. No reporting of data is able to be undertaken within the DrDoctor platform itself and, at the time of feasibility study design, exporting of this information was also not possible. Finally, it was identified that there was a lack of clinical interoperability (transfer of information) possible between DrDoctor and the hospital software systems utilised at Guy's Cancer Centre. This meant that data could only be held within the DrDoctor platform and could not be integrated with the clinical information of patients automatically.

5.3.1.8.2 REDCap

Research Electronic Data CAPture, or REDCap, is described as a secure web-based application which can be utilised to build and manage online surveys and databases (415). The platform was first developed in 2004 at Vanderbilt University by a group of clinical researchers requiring a secure data collection tool which was compliant according to the Health Insurance Portability and Accountability Act (HIPAA). Following initial development, the REDCap consortium was launched in 2006 to facilitate dissemination of the software and foster further research collaborations. The REDCap consortium was set-up primarily to enable international research groups to fully customise their REDCap platforms according to local regulations, personalise functionality as per user needs, and allow input into future versions of the software.

REDCap permits free usage of its software for not for profit and academic institutions on the proviso that each partnering organisation signs an end-user license agreement. Part of the work of this thesis involved onboarding Guy's Cancer Centre as a partner organisation of REDCap and working with relevant IT departments within the hospital Trust to set-up the necessary server infrastructure to house the platform. Following a period of testing, the REDCap platform for Guy's Cancer went live on 1st of March 2021 and I hold the role of Super Administrator for this instance.

REDCap is a multifunctional platform which boasts features including automated survey invitations, interoperability with electronic health record platforms, and a mobile application which is available on iOS and Android. For the purposes of this feasibility study, the automated survey invitation functionality was employed to trigger patient follow-up via emails according to the follow-up

schedule agreed in section 5.3.1.6. A caveat of the platform is that an email address is required to be inputted for patients to enable automated follow-up and, prior to the COVID-19 pandemic, email addresses were not routinely collected within clinical settings. During the COVID-19 pandemic, however, there was a perhaps perpetual paradigm shift towards remote telemedicine which facilitated the inclusion of email addresses within the patient health records. As part of this feasibility study, and to ensure accuracy of contact details, the email addresses of the patients opting for electronic collection were collated by the radiographers at time of recruitment.

For patients completing their PROMs using pen and paper, questionnaire responses were entered into the REDCap database by either myself or the radiographers. REDCap assigns a unique patient ID to every record added onto the platform, and this ID was employed to link the follow-up EPIC-26 questionnaires with the baseline event. The calendar feature of the platform was used specifically for the patient group completing their PROMs with pen and paper to monitor when the next follow-up questionnaires were due. For the patient cohort completing electronic PROMs (ePROMs), the REDCap platform was set-up to trigger reminder emails if the EPIC-26 questionnaire had not been completed 3 days, and then 6 days, after initial sending.

The feasibility study was set-up within REDCap to automatically transform the Likert responses of EPIC-26 into the linear 0-100 score as outlined above in section 5.3.1.5. Calculated fields were set-up to automatically populate the subscale mean summary scores per EPIC-26 domain. Following completion of the EPIC-26 questionnaire, a PDF of the responses, including the raw scores and mean summary scores, was automatically generated per record. This PDF document was able to be one-click downloaded for review by the clinical teams or for later upload onto the electronic health records.

Additional functionality of REDCap includes the availability of basic statistics and chart reporting within the platform itself. Patient responses and mean summary scores can be plotted and viewed in a comparative fashion against the scores of other records. Furthermore, data is able to be exported from REDCap in comma-separated values (CSV) format into various statistical analysis packages including *R* studio, Stata and SAS.

5.3.2 Feasibility study overview

In summary, a pilot study of routine clinical PROM collection was developed for a consecutive population of prostate cancer patients receiving radiotherapy treatment at Guy's Cancer Centre. This feasibility study was developed as the first exploratory attempt to implement PROMs at this site and included process evaluation to determine the barriers and facilitators impacting implementation success. Although undertaken solely in the prostate cancer setting, the feasibility study aimed to

identify the most critical contextual factors for consideration when implementing PROMs in routine clinical cancer settings. The feasibility study was established in one tumour setting alone for efficiency, however identified findings are also relevant and require consideration when implementing routine PROM collection across tumour settings.

This pilot commenced with recruitment of patients from August 2021 to March 2022 and the EPIC-26 questionnaire was collated at predefined timepoints prior to and following completion of radiotherapy. The REDCap platform was selected to manage the collection of PROMs and patients were able to opt for electronic completion or pen and paper completion based on their needs. The EPIC-26 PROM was scored automatically within REDCap and key stakeholders were provided user permissions to view this data for clinical management. I worked closely with these stakeholders to design, develop and undertake this feasibility study.

The following section of this thesis reports some of the results of this feasibility study. Specifically, data related to patient outcomes and the effectiveness of this feasibility study of routine clinical PROM collection are presented. Quantitative and qualitative evaluation of this feasibility study is subsequently reported in Chapter VI.

5.3.3 Data handling and analysis

Data related to the demographics of the patients included within this feasibility study was collated utilising the electronic health record systems of Guy's and St Thomas' NHS Foundation Trust. Specifically, information on patient date of birth, ethnicity, date of prostate cancer diagnosis, PSA score at diagnosis, Gleason score at diagnosis, tumour staging at diagnosis and postcode was extracted. These datapoints were applied to provide high level insight into the characteristics of the patient population recruited to the feasibility study.

Note, postcode was utilised as a proxy for calculating the socioeconomic status of the patients. The postcodes of the patient population were entered into the English indices of deprivation 2019 tool (<https://imd-by-postcode.opendatacommunities.org/imd/2019>) and translated into indices of deprivation, scored from 1-10. Following collation of the indices of deprivation scores, these scores were grouped to reflect Low, Middle, and High socioeconomic status. Overall, indices between 1-3 were transformed to Low socioeconomic status, 4-7 indicated Middle socioeconomic status, and 8-10, High.

Data collated throughout the feasibility study was predominantly analysed descriptively. Mean scores for each subscale of EPIC-26 were calculated per patient, in line with the published scoring manual of the PROM, before population-level averages were determined. Both population-level and

patient-level average subscale scores were compared against the minimally important differences defined by Skolarus et al (413). Data management and descriptive analysis were carried out using Microsoft Excel.

5.4 Results

5.4.1 Patient demographics

In total, 20 prostate cancer patients who received radiotherapy treatment for their disease were recruited at Guy's Cancer Centre. The patients' end of radiotherapy treatment date ranged from 10th August 2021 to 22nd March 2022. Patient characteristics are presented below in Table 27.

Table 27: Characteristics of prostate cancer patients recruited to the feasibility study of routine clinical PROM collection at Guy's Cancer Centre.

	N = 20 (N (%))
Mean age at baseline (s.d.)	68.01 (7.90)
Age at baseline	
50-54	1 (5.0)
54-59	3 (15.0)
60-64	2 (10.0)
65-69	4 (20.0)
70-74	6 (30.0)
75-79	3 (15.0)
80-84	1 (5.0)
Mean age at diagnosis (s.d.)	66.97 (8.02)
Age at diagnosis	
50-54	1 (5.0)
54-59	4 (20.0)
60-64	3 (15.0)
65-69	4 (20.0)
70-74	4 (20.0)
75-79	3 (15.0)
80-84	1 (5.0)
Ethnicity	
White	14(70.0)
Black	5 (25.0)
Asian	0 (0.0)
Mixed	1 (5.0)
Other	0 (0.0)
Mean PSA at Dx (s.d.)	9.43 (6.47)
Gleason score @ Dx	
3 + 4	6 (30.0)
4 + 3	8 (40.0)
3 + 5	1 (5.0)
4 + 4	1 (5.0)
4 + 5	4 (20.0)
Tumour Stage	
T2a N0	9 (45.0)
T2c N0	1 (5.0)
T2 N0	6 (30.0)
T3a N0	2 (10.0)
T3b N0	1 (5.0)
T3a N1	1 (5.0)
Socioeconomic status	
Low	8 (40.0)
Middle	8 (40.0)
High	4 (20.0)

The mean age of the patients at completion of the baseline EPIC-26 questionnaire was 68.01 (SD 7.90) years. Fourteen of the males were of White ethnicity, five of the patients were Black and one patient was of Mixed ethnicity. The mean PSA score for the patients at diagnosis was 9.43 (SD 6.47) and most patients (70%) had Gleason score 7 disease (comprising 3+4 or 4+3 classification). Almost half of the patients were diagnosed with prostate cancer classified as stage T2a N0. In terms of socioeconomic status, which was calculated using postcode as a proxy, 16 of the patients were of low or middle socioeconomic status.

5.4.2 EPIC-26 subscale mean scores

As described in section 5.3.1.5, at each timepoint of follow-up a mean score was calculated per patient for each subscale or domain of the EPIC-26 questionnaire. Overall, the EPIC-26 questionnaire comprises 5 domains including urinary incontinence, urinary irritative, bowel, sexual and hormonal/vitality. The mean scores were calculated per subscale of EPIC-26 and are reported below, per patient and at each timepoint, in Tables 28-32.

Table 28: Mean urinary incontinence subscale scores per patient and at each timepoint of feasibility study follow-up. The population average for each timepoint is included along with a calculation of the difference between means at each successive timepoint (to compare against the calculated minimally important differences for EPIC-26). Missing data, attributed to non-compliance with PROM completion, is presented as ‘-’.

Record ID	Baseline	6-weeks	3-months	6-months	1-year
1	91.75	66.75	79.25	79.25	79.25
2	71.00	-	-	-	-
3	100.00	100.00	100.00	100.00	-
4	100.00	-	-	-	-
5	85.50	-	85.50	85.50	66.75
6	100.00	85.50	-	85.50	100.00
7	93.75	91.75	100.00	-	93.75
8	100.00	100.00	100.00	100.00	100.00
9	100.00	100.00	100.00	100.00	91.75
10	75.00	-	-	-	-
11	93.75	73.00	68.75	100.00	75.00
12	100.00	85.50	-	-	79.25
13	85.50	100.00	100.00	100.00	100.00
14	100.00	66.75	-	-	-
15	100.00	-	-	66.75	-
16	100.00	-	100.00	100.00	100.00
17	100.00	-	100.00	100.00	-
18	85.50	79.25	79.25	100.00	66.75
19	100.00	-	-	100.00	-
20	100.00	-	-	-	-
Average	94.09	86.23	92.07	93.62	86.59
MIDs		- 7.86	+ 5.84	+ 1.55	- 7.03

Prior to radiotherapy treatment, the population average urinary incontinence score was 94.09. At 6-weeks post end of radiotherapy treatment, the average decreased to 86.23 representing a reduction of 7.86 points. According to the minimally important difference (MID) or change in EPIC-26 scores for urinary incontinence, a difference of 6-9 points would indicate patients necessitating further clinical management. Between the baseline and 6-weeks post radiotherapy timepoints, patients 1, 6, 11, 12, 14, and 18 noted a decrease in their urinary functioning in terms of continence and would, therefore, have been candidates for further clinical management or intervention. Many of these patients experienced a change in scores far above the upper limit of the defined MID (change in score > 9 points).

Between the 6-weeks and 3-months, and 3-months and 6-months timepoints, the population average score for urinary incontinence increased and individual patient scores followed a trend

towards improvement. The average score however fell again at 1-year post radiotherapy treatment from a population high of 93.62 to 86.59. This difference of -7.03 points was also within the MID range of 6-9 points for this subscale and the decrease in mean score could primarily be attributed to patients 5, 9, 11, and 18.

Table 29: Mean urinary irritative subscale scores per patient and at each timepoint of feasibility study follow-up. The population average for each timepoint is included along with a calculation of the difference between means at each successive timepoint (to compare against the calculated minimally important differences for EPIC-26). Missing data, attributed to non-compliance with PROM completion, is presented as ‘-’.

Record ID	Baseline	6-weeks	3-months	6-months	1-year
1	62.50	62.50	62.50	75.00	87.50
2	100.00	-	-	-	-
3	93.75	93.75	100.00	93.75	-
4	100.00	-	-	-	-
5	75.00	-	68.75	75.00	62.50
6	100.00	81.25	-	81.25	87.50
7	93.75	100.00	93.75	-	93.75
8	100.00	50.00	81.25	93.75	93.75
9	100.00	81.25	93.75	87.50	100.00
10	62.50	-	-	-	-
11	100.00	100.00	100.00	87.50	93.75
12	93.75	75.00	-	-	100.00
13	100.00	100.00	100.00	100.00	100.00
14	75.00	56.25	-	-	-
15	100.00	-	-	100.00	-
16	87.50	-	93.75	93.75	100.00
17	93.75	-	100.00	100.00	-
18	87.50	68.75	81.25	81.25	62.50
19	93.75	-	-	100	-
20	87.50	-	-	-	-
Average	90.31	78.98	88.64	89.90	89.20
MIDs		- 11.33	+ 9.66	+ 1.26	- 0.7

The average urinary irritative subscale score for the prostate population was 90.31 at baseline. Similarly with urinary incontinence, the average score decreased significantly at the 6-week timepoint to 78.98, representing a reduction of 11.33 points. The defined MID for the urinary irritative scale is 5-7 points and therefore the decrease in population-level averages lay above the upper limit of the MID change. Patients 8, 9, 12, 14, and 18 all observed significant decreases in their urinary irritative scores at 6 weeks when compared to baseline and may have benefited from further clinical management for such symptoms. After the 6-week timepoint, the population average urinary

irritative scores increased at 3-months and 6-months suggesting that such symptoms may have alleviated. Despite the population average increase, specific patients reported worsening symptoms at these timepoints when compared to previous administration of EPIC-26. For example, at 3-months follow-up patient 7's subscale score was 93.75 compared to a score of 100 at the 6-week timepoint. Similarly, at 6-months, patients 3, 9, and 11 described worsened urinary irritative symptoms compared to the 3-month timepoint. The population average declined slightly at 1-year by 0.7 but overall scores remained high across the full post-radiotherapy period. At the 1-year timepoint patients 5 and 18 noted a decrease in their urinary irritative subscale scores, when compared to the 6-month PROM administration. These patients may have been suitable candidates for further clinical management.

Table 30: Mean bowel subscale scores per patient and at each timepoint of feasibility study follow-up. The population average for each timepoint is included along with a calculation of the difference between means at each successive timepoint (to compare against the calculated minimally important differences for EPIC-26). Missing data, attributed to non-compliance with PROM completion, is presented as '-'.

Record ID	Baseline	6-weeks	3-months	6-months	1-year
1	83.33	66.67	50.00	66.67	62.50
2	100.00	-	-	-	-
3	95.83	95.83	100.00	100.00	-
4	100.00	-	-	-	-
5	100.00	-	83.33	79.17	70.83
6	100.00	95.83	-	95.83	95.83
7	83.33	95.83	87.50	-	95.83
8	100.00	100.00	100.00	100.00	100.00
9	100.00	100.00	95.83	95.83	100.00
10	87.50	-	-	-	-
11	100.00	100.00	100.00	100.00	100.00
12	100.00	83.33	-	-	100.00
13	100.00	100.00	100.00	100.00	100.00
14	83.33	66.67	-	-	-
15	100.00	-	-	95.83	-
16	91.67	-	100.00	87.50	87.50
17	95.83	-	100.00	100.00	-
18	100.00	91.67	100.00	95.83	95.83
19	100.00	-	-	100.00	-
20	100.00	-	-	-	-
Average	96.04	90.53	92.42	93.59	91.67
MIDs		- 5.51	+ 1.89	+ 1.17	- 1.92

Overall, the bowel subscale scores remained high (average > 90) across the feasibility study period. At baseline, and prior to radiotherapy treatment, the population bowel score was 96.04. Following the 6-week EPIC-26 administration, the population average reduced by 5.51 points to 90.53 compared to the baseline average. The MID range for bowel symptoms was calculated by Skolarus et al as a change in score of 4-6 points (413). The decrease in average score between baseline and 6-weeks follow-up therefore lay within the defined MID range. Significant declining bowel functioning was observed for patient 1, 6, 12, 14, and 18 at the 6-week timepoint. By the 3-month follow-up, seven patients reported no bowel symptoms translating into scores of 100 for this subscale. However, patients 1, 7, and 9 presented continued worsening of bowel symptoms at this timepoint compared to 6-weeks. As was observed with the urinary subscales, at 1-year follow-up the population average bowel scores decreased slightly and remained below the averages calculated at baseline. Indeed, a decline in score was attributed to patients 1 and 5 and both had lower scores compared to the rest of population.

Table 31: Mean sexual subscale scores per patient and at each timepoint of feasibility study follow-up. The population average for each timepoint is included along with a calculation of the difference between means at each successive timepoint (to compare against the calculated minimally important differences for EPIC-26). Missing data, attributed to non-compliance with PROM completion, is presented as ‘-’.

Record ID	Baseline	6-weeks	3-months	6-months	1-year
1	26.33	41.67	32.00	48.67	26.33
2	30.50	-	-	-	-
3	26.33	-	-	-	-
4	29.17	-	-	-	-
5	4.17	-	0.0	0.0	0.0
6	16.67	-	-	16.67	16.67
7	0.0	22.17	8.33	-	18.00
8	4.17	0.0	44.50	26.33	62.50
9	16.67	19.50	4.17	4.17	0.0
10	16.67	-	-	-	-
11	20.83	30.50	12.50	41.67	16.67
12	61.17	65.33	-	-	52.83
13	0.0	0.0	0.0	0.0	0.0
14	41.67	16.67	-	-	-
15	0.0	-	-	13.83	-
16	16.67	-	0.0	16.67	16.67
17	22.17	-	30.50	22.17	-
18	12.50	18.0	13.83	16.67	9.67
19	0.0	-	-	0.0	-
20	26.33	-	-	-	-
Average	18.60	23.76	14.6	17.24	19.94
MIDs		+ 5.16	- 9.16	+ 2.64	+ 2.70

Overall, the average sexual subscale scores measured during the feasibility study were significantly lower at all timepoints compared to the other subscales assessed using EPIC-26. At baseline, the sexual score was 18.60 suggesting that sexual functioning of the study population was low prior to commencement of radiotherapy treatment. Interestingly, the population average score increased at 6-weeks by 5.16 points suggesting an improvement in symptoms of sexual functioning across the prostate patients. One patient, record 14, however noted a significant worsening of sexual symptoms at 6-weeks compared to baseline of 25 points. The calculated MID for the sexual subscale ranged from 10-12 points highlighting that patient 14 experienced a change outside the upper limit of this MID. At the 3-month timepoint, the population average sexual subscale score decreased by 9.16 points from 23.76 at 6-weeks to 14.6. Such decline did not reach the threshold for the MID but, at the individual patient level, several patient’s score change did either fall within the MID range or exceed it. Indeed, patients 7, 9, and 11 experienced a significant decrease in sexual functioning at 3-

months when compared to their scores at 6 weeks post radiotherapy. After the 3-month timepoint, the population average sexual subscales followed an upward trend improving by 2.64 points at 6-months and 2.70 points at 1-year.

Table 32: Mean hormonal subscale scores per patient and at each timepoint of feasibility study follow-up. The population average for each timepoint is included along with a calculation of the difference between means at each successive timepoint (to compare against the calculated minimally important differences for EPIC-26). Missing data, attributed to non-compliance with PROM completion, is presented as ‘-’.

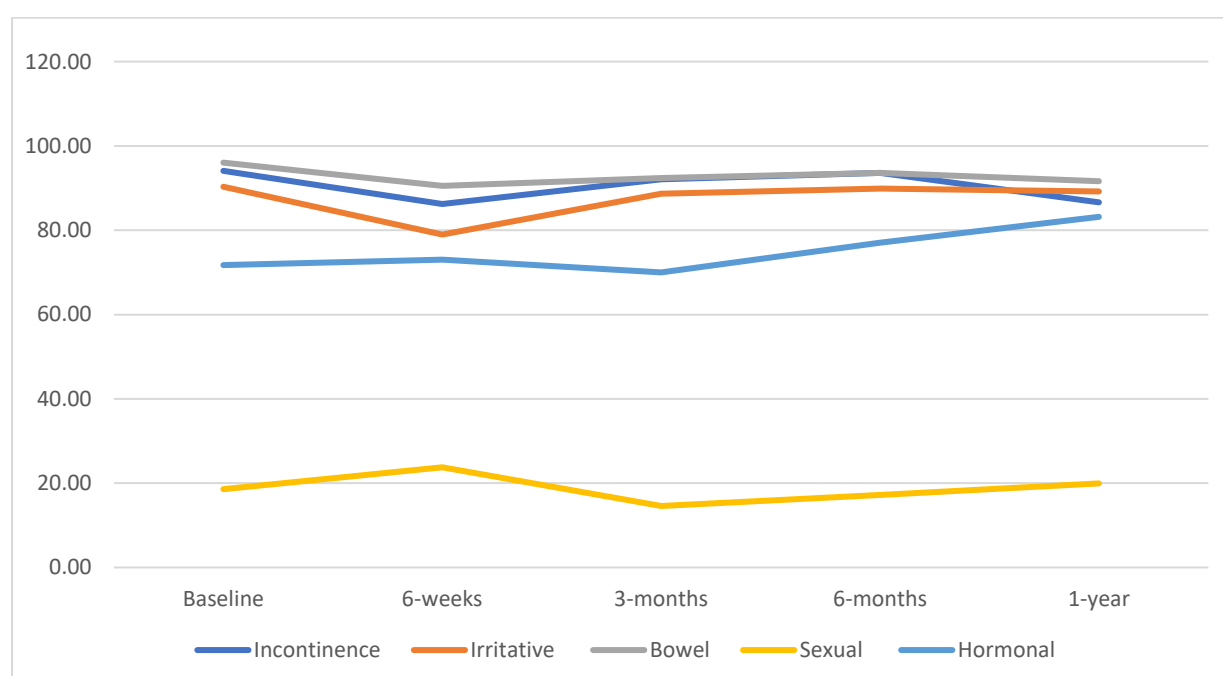
Record ID	Baseline	6-weeks	3-months	6-months	1-year
1	60.00	55.00	65.00	70.00	65.00
2	70.00	-	-	-	-
3	100.00	-	-	-	-
4	85.00	-	-	-	-
5	40.00	-	45.00	70.00	65.00
6	85.00	95.00	-	95.00	100.00
7	65.00	70.00	75.00	-	90.00
8	85.00	80.00	95.00	100.00	100.00
9	80.00	85.00	75.00	75.00	100.00
10	20.00	-	-	-	-
11	90.00	100.00	75.00	90.00	95.00
12	85.00	85.00	-	-	85.00
13	40.00	35.00	15.00	40.00	55.00
14	65.00	65.00	-	-	-
15	95.00	-	-	85.00	-
16	85.00	-	85.00	90.00	90.00
17	75.00	-	95.00	90.00	-
18	65.00	60.00	75.00	65.00	70.00
19	55.00	-	-	55.00	-
20	90.00	-	-	-	-
Average	71.75	73	70	77.08	83.18
MIDs		+ 1.25	- 3.0	+ 7.08	+ 7.35

Finally, in terms of the hormonal subscale of EPIC-26, the population average scores ranged from 71.75 at baseline to 83.18 at 1-year post radiotherapy. The calculated MID for this subscale ranged from 4-6 points change but was not reached at any timepoint across the follow-up journey, when appraising the population means. Some individual patients did see decreases in their vitality functioning at each timepoint, noticeably patients 1, 8, 13, and 18 all reduced in score by 5 points between baseline and 6-weeks. Such a drop in score highlights that these patients may have benefitted from further clinical intervention. Additionally, between the 6-week and 3-month timepoints the average score declined by 3 points. At the 3-month mark post radiotherapy, 3

patients reported a marked reduction in their vitality scores when compared to the previous timepoint. Despite this, at the 6-month and 1-year timepoints the population average scores observed an upward trend to 83.18. Most patients reported improvements to their hormonal functioning at these timepoints, except for patients 1 and 5 who's scores decreased by 5 points each (70 to 65).

Following the individual appraisal of each subscale of the EPIC-26, the population-level summary means were subsequently mapped for each domain and at each timepoint of follow-up. This graph is presented below in Figure 8 and provides visual context for the population averages of each domain of health-related quality of life across the defined follow-up.

8. Figure 8: Mapping of the population-level summary scores for each domain of EPIC-26, and at each timepoint of administration.



As described above, population averages for sexual functioning were consistently lower than the mean scores for urinary incontinence, urinary irritative, bowel and hormonal functioning. The summative means for the sexual domain persisted around a score of 20 across each timepoint of follow-up, and no major improvements in functioning were observed at the population level. In comparison, population average scores for the bowel and urinary subscales were highest throughout the duration of follow-up, until the 1-year timepoint. For the sexual, hormonal, and urinary irritative domains, an overall improvement in symptoms was observed when comparing baseline pre-treatment population-level scores with the averages at 1-year post end of radiotherapy. In contrast, the summary means observed at 1-year follow-up for the urinary incontinence and bowel domains presented a decrease in functioning, or worsening of symptoms, at the population level compared to

baseline scores. Overall, compared to baseline, urinary incontinence, urinary irritative and bowel symptoms worsened at the 6-week timepoint whereas sexual and hormonal symptoms slightly improved.

5.5 Discussion

This study was conducted to describe the outcomes and effectiveness of the feasibility study of EPIC-26 completion which was undertaken with prostate cancer patients in the radiotherapy setting at Guy's Cancer Centre. Summary scores for each subscale of EPIC-26 were calculated per patient according to the scoring manual of the questionnaire before population-level means were assessed and compared at each timepoint of administration. Overall, at the population-level, the sexual functioning of the patients remained low throughout the duration of follow-up. Similarly, scores associated with vitality averaged around the low 70s until 6-months post radiotherapy, when improvement was observed, and scores reached the low 80s at the 1-year administration. In terms of bowel symptoms, the patient cohort overall reported low levels of toxicity and scores remained above 90 points at each timepoint of follow-up. Regarding the urinary subscales, patients experienced a worsening of symptoms at the 6-week timepoint following completion of radiotherapy before an overall trend towards symptom improvement was observed at each subsequent timepoint.

The majority of patients recruited to the feasibility study had T2 N0 localised disease. As described above in section 2.2.3.5, for patients with localised disease, radical radiation therapy with androgen deprivation therapy (ADT) is an acceptable multimodal combination of treatments for patients with such disease.

The majority of feasibility study patients reported sexual dysfunction prior to commencement of radiotherapy, indicating that significant toxicity was experienced following commencement of neoadjuvant ADT (126, 416). Additionally, sexual functioning declined further and remained low following completion of radiotherapy, providing evidence that radiotherapy can impair sexual functioning and can lead to erectile dysfunction. Specifically, across all timepoints of follow-up, the majority of patients reported that their ability to have an erection was poor or very poor to none, and that the quality of their erections was none at all, or not firm enough for any sexual activity. Additionally, across all timepoints of follow-up, no patient indicated that their orgasmic function was good or very good. Indeed, the majority of patients observed that their ability to reach orgasm was poor, or very poor to none.

Such results support literature findings that more than 75% of prostate cancer patients experience sexual dysfunction, and approximately 60% report significant emotional distress related to sexual

dysfunction (417). Within the NHS, current treatment guidelines recommend early intervention and provision of a choice of five options including referral to an NHS erectile dysfunction clinic, an appropriate choice of medication such as tadalafil, vacuum pumps, psychosexual clinics, and counselling services. A freedom of information request by Prostate Cancer UK however identified that only 51% of commissioners offer an erectile dysfunction clinic and as few as 25% of men were offered support or medication to manage sexual dysfunction arising from prostate cancer therapy (5). The outcomes reported in this feasibility study further highlight the necessity to provide ongoing supportive care for prostate cancer patients including the implementation of long-term follow-up clinics tailored for toxicity management specifically within NHS settings.

Secondly, in this study of EPIC-26 administration prior to and following completion of radiotherapy, most patients did not experience severe toxicity in terms of urinary continence. Across each timepoint of follow-up, patients noted that, in the 4 weeks prior to questionnaire completion, they had rarely or never experienced leaking of urine. Additionally, most patients reported total urinary control and did not require use of any pads for urinary leakage. The outcomes of the feasibility study, in terms of urinary incontinence, therefore align with published literature concluding that ADT use does not negatively impact lower urinary tract symptoms (418). Additionally, a study of 758 men who received definitive external-beam radiation therapy identified that urinary incontinence was a rare event in clinically localised prostate cancer, and the results of this EPIC-26 feasibility study provides data to support this further (419).

Interestingly, the ProtecT trial identified bowel toxicity, in the form of persistent diarrhoea, increased urgency of bowel movements, faecal incontinence, and/or rectal bleeding, as the most reported side effect of radiation therapy (121). Contrastingly, in this feasibility study of EPIC-26 collection after radiation therapy, bowel functioning remained high across each timepoint of follow-up. Although some patients reported moderate problems with bowel movement urgency, and increased frequency of bowel movements, nearly all patients described having either no problem or a very small problem with their bowel habits across the follow-up period of the study. The results of this study align with The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study who used the EPIC-26 questionnaire across treatment modalities and observed that decline in bowel domain score was not commonly observed (420). As discussed in the CAESER study, the ProtecT study population was formed of 99% Caucasian males with 80% of patients with Gleason 6 disease and 87% undergoing open radical prostatectomy prior to radiation therapy. Therefore, the results of the ProtecT study are not generalisable to this study which had a racially diverse population and involved radiation therapy plus ADT combination therapy rather than open radical prostatectomy.

Moreover, in terms of hormonal domain scores, the results of this study align with the feasibility study participants commencing neoadjuvant and concurrent ADT therapy prior to radiation therapy. Alongside loss of libido and erectile dysfunction, ADT therapy has been shown to cause hot flushes, feelings of depression, fatigue, and weight gain (126, 130, 131). Population mean scores for vitality were 71.75 at baseline indicating that the side effects of ADT were established prior to commencement of radiation therapy. Population means then improved (to 77.08 and 83.18) after the 6-month timepoint of follow-up in line with a proportion of patients being prescribed ADT for a 6-month period only (compared to 3-years). The impact of hormonal therapy, observed in this feasibility study, highlights a need for introduction of further management strategies to maintain patient quality of life in terms of vitality. Some evidence exists to suggest a role for implementation of exercise programs during combination radiotherapy and ADT treatment. Such strategies have demonstrated improvements in cardiovascular symptoms and muscle function (421). Additionally, nurse-led multidisciplinary rehabilitation exhibited a positive impact on sexual functioning and cancer worry for men with localised prostate cancer (422).

This study utilised minimally important differences (MIDs), as defined by Skolarus, to examine the impact of radiation therapy and ADT on patient functioning and outcomes. Although MID ranges provide important insight into patient toxicity at the subscale level, they lack sensitivity to highlight specific side effects or symptoms which may be of greater burden to the patient. For example, the vitality subscale of EPIC-26 is formed of five individual side effects which may occur simultaneously but require differing management strategies to alleviate symptoms. The MID ranges do not provide such insight into specific symptoms which may be impacting the overall subscale score, but rather provide an overall picture of functioning at the domain level.

Additionally, MIDs offer a reference for interpreting changes in scores over time but do not aid in the interpretation of absolute scores gained at a single point in time (423). For these purposes, it is necessary to define thresholds for clinical importance to screen for clinically important symptoms in daily practice. Moreover, the results of this study do not incorporate data on what value patients place on particular domains or symptoms. At the point of undertaking of this feasibility study, no thresholds for clinical importance had been defined in the literature. This lack of defined thresholds posed a further barrier in the implementation of routine clinical PROM collection as multiple timepoints of EPIC-26 completion were required to calculate MIDs. Patient compliance is discussed in detail in section 6.2, however emerged as a limitation in this feasibility study. Therefore, the definition of well-defined and valid absolute thresholds, which are of value to patients, arose as an implementation strategy in this thesis to facilitate implementation scale-up and sustainability. This

implementation strategy is required to be developed systematically, and utilising consensus processes involving both healthcare professionals and patients.

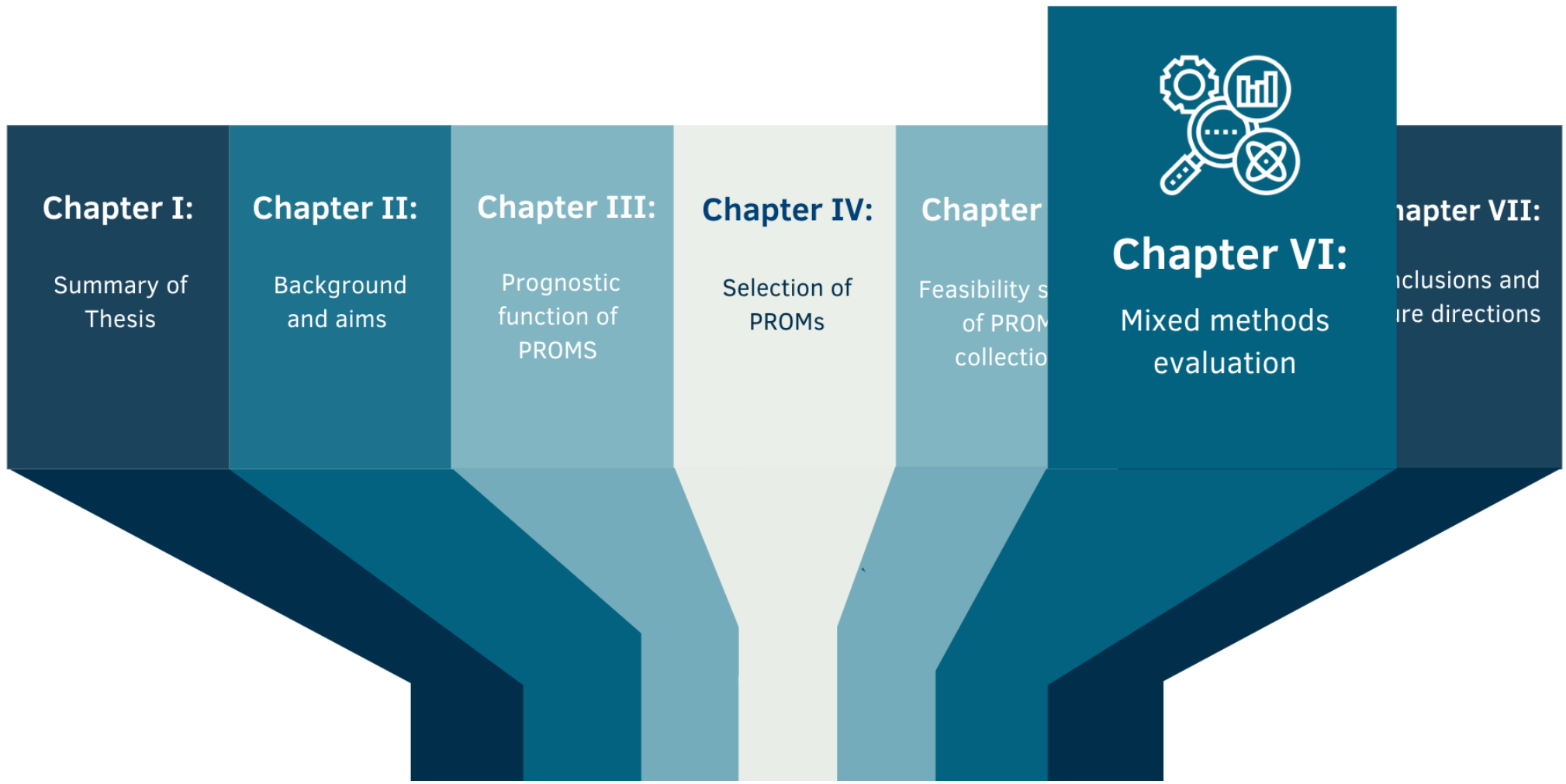
5.6 Conclusions

This study involved the development and undertaking of a feasibility study of routine clinical PROM collection for a consecutive series of prostate cancer patients treated with combination radiation therapy and androgen deprivation therapy. In total, 20 patients were recruited and completed the EPIC-26 questionnaire at timepoints prior to and following completion of radiotherapy. Overall, sexual domain scores were significantly lower than the four alternate measured domains and remained low over the course of follow-up. Additionally, and in line with the prescription of neoadjuvant and concurrent ADT, the recruited patients highlighted toxicity related to symptoms of vitality. This study highlights the value of utilising PROMs in the routine clinical setting to measure and quantify patient toxicity. Further work is, however, required to develop rehabilitation clinics to alleviate symptom burden and to define absolute thresholds for clinical importance which can be employed at single timepoints to determine patients requiring such management.

Chapter VI:

Mixed methods evaluation

This chapter involves qualitative and quantitative process evaluation of the feasibility study described in Chapter V. Feasibility study evaluation was undertaken to identify contextual factors impacting implementation success, scale-up and sustainability, and emerging strategies to overcome such barriers are described.



6. Chapter VI: Mixed methods evaluation of the feasibility study

6.1 Qualitative feasibility study evaluation

6.1.1 Rationale

There is a growing body of evidence in the literature to support the use of qualitative methods alongside more traditional quantitative methodology to enhance clinical research. In recent years, various published studies have successfully employed qualitative methods for this purpose. One published review of 296 journal articles published between 2008-2010 reported that 28% of randomised controlled trial studies incorporated evaluative qualitative research prior to implementation of a full trial (424). For example, Donovan et al used in-depth participant interviews in the ProtecT (prostate testing for cancer and treatment) feasibility study to investigate the process of recruitment to the trial (425). In this study, men with localised prostate cancer were interviewed after receiving their prostate-specific antigen results and diagnosis. Initial qualitative findings from these interviews elicited that healthcare providers experienced issues with equipoise related to presenting treatments equally, as well as unknowingly using language which could be misinterpreted by patients. As a result of this interview study, changes to the presentation of treatment information were implemented which, in turn, resulted in more efficient recruitment processes which were acceptable to patients and providers. In addition, Verhoef et al further described the benefits of including qualitative research methods within randomised controlled trials (RCTs) in the context of complementary and alternative medicine (426). The authors argued that RCTs generally only address the statistical effect of an intervention, and do not explore why the intervention works, how participants experience the intervention, and how they give meaning to these experiences. Overall, the authors concluded that collation of information related to participant circumstances can increase both understanding of the feasibility study and awareness of intervention burden.

Moreover, in the cancer palliative care setting, Jack and colleagues combined qualitative and quantitative methods to explore the impact of a hospital-based palliative care team on cancer patient's understanding of their disease and prognosis (427). In total, 31 semi-structured interviews were conducted with healthcare providers, and results indicated that patients who had additional input from the palliative care team exhibited significantly improved insight of their diagnosis. The authors advocated the inclusion of a qualitative component in future studies of palliative care in the cancer setting.

Finally, a study by Majumdar et al explored the use of an 8-week mindful meditation programme for 21 participants with chronic physical, psychological, or psychosomatic illnesses (428). Overall,

qualitative data gathered from participant interviews revealed that suffering was significantly alleviated by the mindful meditation programme, and the authors further concluded that there exists an urgent need for research evaluating the efficacy, appropriateness, and cost-effectiveness of intervention programmes within medical settings.

Overall, it is accepted that appropriate and well-conducted qualitative research can form an integral component of feasibility studies when the aim is to improve the intervention prior to full implementation and facilitate future scale-up and dissemination. This qualitative interview study was therefore undertaken to evaluate the feasibility study described in Chapter V and to identify contextual factors contributing to, or impacting, the success of implementation. The Consolidated Framework for Implementation Research (CFIR) was applied in the development and analysis of semi-structured interviews which were conducted with healthcare professionals involved both in the feasibility study and in the wider programme of PROM implementation at Guy's Cancer Centre. Contextual factors impacting routine clinical PROM collection were collated to facilitate subsequent refinement of the programme through identification of tailored implementation strategies specific to this site. The Expert Recommendations for Implementing Change (CFIR-ERIC) compilation was utilised to map discrete implementation strategies against identified barriers.

6.1.2 Methods

6.1.2.1 Study design

A qualitative interview study was designed to identify barriers and facilitators impacting the routine clinical collection of patient-reported outcome measures (PROMs) at Guy's Cancer Centre.

6.1.2.2 Ethical approval

This study was conducted utilising service evaluation approval which was sought from Guy's and St Thomas' NHS Foundation Trust. The service evaluation application form was submitted in May 2021 (Project number: 12416, Title: Gaining stakeholder insight into perceived barriers and facilitators to routine collection of patient-reported outcome measures, and developing understanding of patient experience), and the study received the necessary clearances to commence in July 2021. Service evaluation was deemed appropriate for the purposes of this study as the qualitative interview study sought to define and evaluate the feasibility study implemented in Chapter V. It is anticipated that the implementation of PROM collection at Guy's Cancer Centre will ultimately become routine which is an aim which aligns with the overarching vision and strategy of Guy's and St Thomas' NHS Foundation Trust.

6.1.2.3 Theoretical framework

The semi-structured interview guide was developed using the Consolidated Framework for Implementation Research (CFIR). A detailed background of the CFIR was provided in section 5.1.2, but, briefly, the framework comprises five domains incorporating selectable constructs which influence implementation effectiveness. In the context of this thesis, the CFIR was selected as it is well suited for complex, multilevel interventions such as the local implementation of routine clinical PROM collection at Guy's Cancer. Open-ended interview questions were developed using the interview guide tool of the overarching CFIR guide website (cfirguide.org). Questions covering the five domains of the CFIR (intervention characteristics, inner setting, outer setting, characteristics, and process) were adapted to assess implementation and sustainability, and the interview topic guide is included below within Appendix VIII.

6.1.2.4 Sampling and data collection

In order to gather data on the feasibility study described in Chapter V and explore the potential for scale-up and dissemination, key stakeholders employed at Guy's Cancer Centre were recruited. Potential participants were identified using selective sampling; participants were recruited in a non-randomised fashion according to the aims of the research project (429). For the purposes of this study, stakeholders involved in the development and undertaking of the feasibility study were recruited, as well as stakeholders who had previous external experience of PROM implementation or aspirations of PROM implementation. Key stakeholders from gynaecology oncology were also prioritised for recruitment, in line with the tumour types selected as use cases in this thesis. Potential participants were contacted initially using email, and recruitment continued until a representative sample of stakeholders, across various job roles, had been attained. In total, 22 stakeholders were approached and 14 agreed to participate. Reasons for not participating included a lack of response after multiple attempts at contact and competing time constraints in terms of clinical commitments.

6.1.2.5 Sample Size

In qualitative research, the concept of saturation was first introduced by Glaser and Strauss in 1999 (430). Glaser et al described saturation in the context of Grounded Theory analysis, whereby each new observation is compared with previous analyses to identify similarities and differences. Outside of the Grounded Theory context, however, little information exists to determine and justify the number of participants necessitated within a qualitative analysis.

Alternatively, various authors have stated that the sample size of a qualitative study should be sufficiently large and varied to elucidate the study aims (431, 432). This principle is, however, flawed

as it provides no robust guidance for study planning. Therefore, Malterud proposed the concept of information power, noting that the larger information power the sample holds, the lower number of participants required, and vice versa (433). According to this model, five items should be considered to determine whether sufficient information power has been obtained; these items comprise the study aim, sample specificity, theoretical background, quality of dialogue, and strategy for analysis. This information power model was employed in the planning of this study to estimate that at least 10 interviews would be required to sufficiently address the study aim and comprehensively identify the contextual factors affecting implementation at this site.

6.1.2.6 Data collection

I conducted all interviews either in person or online, using Microsoft Teams, depending on participant preference. Interviews were completed between October 2021 and August 2022, and were performed concurrently with the on-going feasibility study described in Chapter V. On average, interviews were 26 minutes in length. Interviews were audio-recorded and transcribed verbatim, and I reviewed each file to ensure the quality and accuracy of the data. Finally, the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist was employed to ensure all relevant aspects of qualitative research were reported.

6.1.2.7 Data analysis

Data from each semi-structured interview was analysed utilising an iterative deductive approach. An iterative approach was employed to encourage the adaptation and development of the analysis process, based on learnings from previous analyses' (434). Deductive analysis refers to the application of predetermined codes to the data, and the CFIR was employed in this study as the guiding theory (397). NVivo was used to code each interview and codebooks were developed guided by the constructs of the CFIR. A definition of each of the constructs of the five domains of the CFIR is included below in Table 33, for reference. I coded each transcript independently to categorise data by construct of the CFIR. The codebook was revised as necessary, allowing for the addition of codes which emerged throughout the analysis process. Following finalisation of the data coding, I worked to identify the salient barriers and facilitators, and selected key quotes from the transcripts to represent each contextual factor.

Table 33: Constructs and associated definitions of the Consolidated Framework for Implementation Research, categorised by domain. Adapted from the CFIRguide website: (cfirguide.org)

I. INNOVATION DOMAIN	
Construct Name	Construct Definition <i>The degree to which:</i>
<i>A. Innovation Source</i>	The group that developed and/or visibly sponsored use of the innovation is reputable, credible, and/or trustable.
<i>B. Innovation Evidence-Base</i>	The innovation has robust evidence supporting its effectiveness.
<i>C. Innovation Relative Advantage</i>	The innovation is better than other available innovations or current practice.
<i>D. Innovation Adaptability</i>	The innovation can be modified, tailored, or refined to fit local context or needs.
<i>E. Innovation Trialability</i>	The innovation can be tested or piloted on a small scale and undone.
<i>F. Innovation Complexity</i>	The innovation is complicated, which may be reflected by its scope and/or the nature and number of connections and steps.
<i>G. Innovation Design</i>	The innovation is well designed and packaged, including how it is assembled, bundled, and presented.
<i>H. Innovation Cost</i>	The innovation purchase and operating costs are affordable.
II. OUTER SETTING DOMAIN	
Construct Name	Construct Definition <i>The degree to which:</i>
<i>A. Critical Incidents</i>	Large-scale and/or unanticipated events disrupt implementation and/or delivery of the innovation.
<i>B. Local Attitudes</i>	Sociocultural values (e.g., shared responsibility in helping recipients) and beliefs (e.g., convictions about the worthiness of recipients) encourage the Outer Setting to support implementation and/or delivery of the innovation.
<i>C. Local Conditions</i>	Economic, environmental, political, and/or technological conditions enable the Outer Setting to support implementation and/or delivery of the innovation.
<i>D. Partnerships & Connections</i>	The Inner Setting is networked with external entities, including referral networks, academic affiliations, and professional organization networks.
<i>E. Policies & Laws</i>	Legislation, regulations, professional group guidelines and recommendations, or accreditation standards support implementation and/or delivery of the innovation.
<i>F. Financing</i>	Funding from external entities (e.g., grants, reimbursement) is available to implement and/or deliver the innovation.
<i>G. External Pressure</i>	External pressures drive implementation and/or delivery of the innovation. Note: Use this construct to capture themes related to External Pressures that are not included in the subconstructs below.
<i>1. Societal Pressure</i>	Mass media campaigns, advocacy groups, or social movements or protests drive implementation and/or delivery of the innovation.
<i>2. Market Pressure</i>	Competing with and/or imitating peer entities drives implementation and/or delivery of the innovation.
<i>3. Performance-Measurement Pressure</i>	Quality or benchmarking metrics or established service goals drive implementation and/or delivery of the innovation.
III. INNER SETTING DOMAIN	

Construct Name	Construct Definition <i>The degree to which:</i>
<i>A. Structural Characteristics</i>	Infrastructure components support functional performance of the Inner Setting. Note: Use this construct to capture themes related to Structural Characteristics that are not included in the subconstructs below.
<i>1. Physical Infrastructure</i>	Layout and configuration of space and other tangible material features support functional performance of the Inner Setting.
<i>2. Information Technology Infrastructure</i>	Technological systems for tele-communication, electronic documentation, and data storage, management, reporting, and analysis support functional performance of the Inner Setting.
<i>3. Work Infrastructure</i>	Organization of tasks and responsibilities within and between individuals and teams, and general staffing levels, support functional performance of the Inner Setting.
<i>B. Relational Connections</i>	There are high quality formal and informal relationships, networks, and teams within and across Inner Setting boundaries (e.g., structural, professional).
<i>C. Communications</i>	There are high quality formal and informal information sharing practices within and across Inner Setting boundaries (e.g., structural, professional).
<i>D. Culture</i>	There are shared values, beliefs, and norms across the Inner Setting. Note: Use this construct to capture themes related to Culture that are not included in the subconstructs below.
<i>1. Human Equality-Centeredness</i>	There are shared values, beliefs, and norms about the inherent equal worth and value of all human beings.
<i>2. Recipient-Centeredness</i>	There are shared values, beliefs, and norms around caring, supporting, and addressing the needs and welfare of recipients.
<i>3. Deliverer-Centeredness</i>	There are shared values, beliefs, and norms around caring, supporting, and addressing the needs and welfare of deliverers.
<i>4. Learning-Centeredness</i>	There are shared values, beliefs, and norms around psychological safety, continual improvement, and using data to inform practice.
<i>E. Tension for Change</i>	The current situation is intolerable and needs to change.
<i>F. Compatibility</i>	The innovation fits with workflows, systems, and processes.
<i>G. Relative Priority</i>	Implementing and delivering the innovation is important compared to other initiatives.
<i>H. Incentive Systems</i>	Tangible and/or intangible incentives and rewards and/or disincentives and punishments support implementation and delivery of the innovation.
<i>I. Mission Alignment</i>	Implementing and delivering the innovation is in line with the overarching commitment, purpose, or goals in the Inner Setting.
<i>J. Available Resources</i>	Resources are available to implement and deliver the innovation. Note: Use this construct to capture themes related to Available Resources that are not included in the subconstructs below.
<i>1. Funding</i>	Funding is available to implement and deliver the innovation.
<i>2. Space</i>	Physical space is available to implement and deliver the innovation.
<i>3. Materials & Equipment</i>	Supplies are available to implement and deliver the innovation.
<i>K. Access to Knowledge & Information</i>	Guidance and/or training is accessible to implement and deliver the innovation.
IV. INDIVIDUALS DOMAIN	
Construct Name	Construct Definition

<i>A. High-level Leaders</i>	Individuals with a high level of authority, including key decision-makers, executive leaders, or directors.
<i>B. Mid-level Leaders</i>	Individuals with a moderate level of authority, including leaders supervised by a high-level leader and who supervise others.
<i>C. Opinion Leaders</i>	Individuals with informal influence on the attitudes and behaviors of others.
<i>D. Implementation Facilitators</i>	Individuals with subject matter expertise who assist, coach, or support implementation.
<i>E. Implementation Leads</i>	Individuals who lead efforts to implement the innovation.
<i>F. Implementation Team Members</i>	Individuals who collaborate with and support the Implementation Leads to implement the innovation, ideally including Innovation Deliverers and Recipients.
<i>G. Other Implementation Support</i>	Individuals who support the Implementation Leads and/or Implementation Team Members to implement the innovation.
<i>H. Innovation Deliverers</i>	Individuals who are directly or indirectly delivering the innovation.
<i>I. Innovation Recipients</i>	Individuals who are directly or indirectly receiving the innovation.
CHARACTERISTICS SUBDOMAIN	
Construct Name	Construct Definition: <i>The degree to which:</i>
<i>A. Need</i>	The individual(s) has deficits related to survival, well-being, or personal fulfillment, which will be addressed by implementation and/or delivery of the innovation.
<i>B. Capability</i>	The individual(s) has interpersonal competence, knowledge, and skills to fulfill Role.
<i>C. Opportunity</i>	The individual(s) has availability, scope, and power to fulfill Role.
<i>D. Motivation</i>	The individual(s) is committed to fulfilling Role.
V. IMPLEMENTATION PROCESS DOMAIN	
Construct Name	Construct Definition: <i>The degree to which individuals:</i>
<i>A. Teaming</i>	Join together, intentionally coordinating and collaborating on interdependent tasks, to implement the innovation.
<i>B. Assessing Needs</i>	Collect information about priorities, preferences, and needs of people. Note: Use this construct to capture themes related to Assessing Needs that are not included in the subconstructs below.
<i>1. Innovation Deliverers</i>	Collect information about the priorities, preferences, and needs of deliverers to guide implementation and delivery of the innovation.
<i>2. Innovation Recipients</i>	Collect information about the priorities, preferences, and needs of recipients to guide implementation and delivery of the innovation.
<i>C. Assessing Context</i>	Collect information to identify and appraise barriers and facilitators to implementation and delivery of the innovation.
<i>D. Planning</i>	Identify roles and responsibilities, outline specific steps and milestones, and define goals and measures for implementation success in advance.
<i>E. Tailoring Strategies</i>	Choose and operationalize implementation strategies to address barriers, leverage facilitators, and fit context.
<i>F. Engaging</i>	Attract and encourage participation in implementation and/or the innovation. Note: Use this construct to capture themes related to Engaging that are not included in the subconstructs below.
<i>1. Innovation Deliverers</i>	Attract and encourage deliverers to serve on the implementation team and/or to deliver the innovation.

<i>2. Innovation Recipients</i>	Attract and encourage recipients to serve on the implementation team and/or participate in the innovation.
<i>G. Doing</i>	Implement in small steps, tests, or cycles of change to trial and cumulatively optimize delivery of the innovation.
<i>H. Reflecting & Evaluating</i>	Collect and discuss quantitative and qualitative information about the success of implementation. Note: Use this construct to capture themes related to Reflecting & Evaluating that are not included in the subconstructs below.
<i>1. Implementation</i>	Collect and discuss quantitative and qualitative information about the success of implementation.
<i>2. Innovation</i>	Collect and discuss quantitative and qualitative information about the success of the innovation.
<i>I. Adapting</i>	Modify the innovation and/or the Inner Setting for optimal fit and integration into work processes.

In order to improve the implementation of routine clinical PROM collection at Guy's Cancer, the data inferred from this interview study was subsequently utilised to commence development of tailored implementation strategies designed to overcome the identified barriers. These emerging implementation strategies are included in table format and within the dialogue of the Discussion section of this Chapter (6.1.4).

I worked to review the main themes emerging from the qualitative interviews and draw comparisons with the literature, before selecting relevant implementation strategies based on the identified barriers. As described above, implementation strategies were selected from the Expert Recommendations for Implementing Change (CFIR-ERIC) compilation. In addition, numerous discussions in the form of three informal focus group discussions and two initial interviews were undertaken to garner support for the implementation strategies selected. In total, three internal focus group discussions were held, as well as two meetings with external European sites who had significant experience of implementing PROMs at scale, to generate confirmatory data in support of implementation strategy development.

6.1.3 Results

6.1.3.1 Description of study participants

In total, 14 interviews were conducted with healthcare professionals employed at Guy's Cancer Centre. Ten of the participants were female, and four were male. Of the fourteen participants, all held formal positions within the Cancer Centre: nine of the participants were clinicians, two were radiographers, two held management positions, and one was a clinical nurse specialist. All interviewees agreed to be recorded and were therefore included in the final analysis.

6.1.3.2 Barriers and facilitators to implementing PROMs routinely at Guy's Cancer Centre

The barriers and facilitators identified in this qualitative interview study fell within each of the five domains of the CFIR. The major findings are presented, according to CFIR domain and construct, in Tables 34-38. Note, for ease of interpretation, each Table reflects one domain of the CFIR, and the associated summary text is included alongside each.

6.1.3.2.1 Innovation

Table 34: Innovation domain barriers and facilitators to implementation of routine clinical PROM collection at Guy's Cancer Centre

CFIR domain	Barriers and facilitators to implementation	Seminal quote(s)
Innovation domain - Adaptability	The implementation process will need to be adapted to enable scale-up across Guy's Cancer	"when you roll it out it's going to be a very big scale number of patients, hopefully we'll get that all worked out electronically and there will be some kind of way to highlight that to make that a bit less labour intensive" "Adding in extra elements to the pathway so the time is going to be different and I think that was a concern I had, so that's something, as we get to a number of patients that I need to work out, how we're going to collect that back in, the paper copies" "I think when it gets rolled out, all tumour groups need somebody in a full time post to be doing it"

The interview participants highlighted potential difficulties with scaling up the implementation of routine PROM collection, across further tumour types, owing to the size of the patient population served by Guy's Cancer Centre. There was a general consensus that the implementation process would be required to be adapted from the agreed protocol of the feasibility study, in order to accommodate such patient numbers. Indeed, one healthcare professional observed that the PROM collection process may need to be adapted to solely electronic methods to make it less labour intensive. Additionally, another participant mused that the implementation process may need to be adapted to include a dedicated position to facilitate PROM collection, per tumour type.

6.1.3.2.2 Outer setting

Table 35: Outer setting domain barriers and facilitators to implementation of routine clinical PROM collection at Guy's Cancer Centre

CFIR domain	Barriers and facilitators to implementation	Seminal quote(s)
Outer Setting - Local Conditions	• The implementation process will need to be aligned across Trust sites, tumour types and treatment modalities • It is unclear what the impact of roll out of the new electronic health record platform will be on routine PROM collection	"kind of being really aware of what patients are also receiving outside of this particular service is really, really important, which is another...It would be different for different patient groups particularly with comorbidities and things like, people are in all different sorts of different departments at the same time" "but reducing the burden on the patient's actually essential, to try and think one can do this every three weeks after having chemo, that's bonkers really, to some degree, to be able to do it on on scale" "I think there would need to be alignment" "Do we as an organisation want something that talks to EPIC? Probably" "I think obviously there's lots of changes going on in the Trust with EPIC coming in" "it's really super important and I've been trying to push and push and push and push at the door of MyChart (EPIC) to try to get that sorted"

Outer Setting - External Pressure	• The clinical teams implementing the routine collection of PROMs have many competing time demands	"In terms of clinician collecting them, this all comes down to time doesn't it" "If I didn't have this time it may be...it would be difficult for somebody and their routine role to to be investing the time" "whether we actually have time then to transcribe that into EPR, even if it's only 10 things, it's still a couple of minutes in a quite time, pressured setting" "I guess for for clinicians the key things is is getting support in time to read the the PROMs and act on the PROMs"
Outer Setting domain - Performance- Measurement Pressure	• The routine PROM collection process needs to be aligned with national and international policy • Resource needs to be available to regularly audit the implementation and ensure quality of data	"Yeah and it is, it can be used, it's not just I guess for like patient level, informing clinical consultations but also kind of use patient aggregated data to inform local and national guidelines" "We do, we have use it nationally and internationally" "but the complexity of running a modern cancer service, particularly with the the reporting requirements that we have. COSD, SACT, RDC National Audit, HIC projects" "I think then we should audit, you know, within a few months as to how, you know, what we've collected, what's the quality of that data and, you know, how the patients have, you know, taken it. So I think auditing this is very important from the nursing point of view, from the patients point of view, and from the clinicians point of view." "I think it's very important to audit after a few months to see actually, what the quality of the data is, because there's no point filling in

		a numbers, and numbers, for a year or two years and then realise actually it didn't give us much information"

Overall, the stakeholders reported the competing time demands of healthcare professionals as a key barrier when implementing the routine clinical collection of PROMs. When describing the process of entering PROM data onto electronic health records platforms, one participant observed "whether we actually have time then to transcribe that into EPR, even if it's only 10 things, it's still a couple of minutes in a quite time pressured setting".

A further identified barrier related to the information technology infrastructure of Guy's and St Thomas' NHS Foundation Trust (GSTT). At the time of feasibility study undertaking, the Trust was moving to roll out of a centralised electronic health record system called EPIC, which was scheduled to go-live in April 2023. Uncertainty existed around the functionality of EPIC, and how use of this centralised platform would affect the routine collection of PROMs. One participant stated, "I think obviously there's lots of changes going on in the Trust with EPIC coming in" and another reflected, "Do we as an organisation want something that talks to EPIC? Probably".

Interview participants also raised the necessity of aligning the implementation process across the various sites of GSTT and within treatment regimens. As noted previously, patients of Guy's Cancer are able to undergo different treatment(s) at the various satellite sites of the overarching Trust. Equally, over the course of their treatment journey, cancer patients often receive various modalities of treatment and can be managed by different specialities, concurrently. The observed barrier relates to difficulties in the alignment of strategy across these sites and specialities, and focuses on alleviating patient burden. Indeed, stakeholders mentioned "kind of being really aware of what patients are also receiving outside of this particular service is really, really important, which is another (barrier)...It would be different for different patient groups particularly with comorbidities and things like, people are in all different sorts of different departments at the same time" and "but reducing the burden on the patient is actually essential, to try and think one can do this every three weeks after having chemo, that's bonkers really, to some degree, to be able to do it on on scale".

6.1.3.2.3 Inner setting

Table 36: Inner setting domain barriers and facilitators to implementation of routine clinical PROM collection at Guy's Cancer Centre

CFIR domain	Barriers and facilitators to implementation	Seminal quote(s)
Inner Setting domain - Structural Characteristics	The implementation setting is a large NHS site with increasing patient numbers	"particularly somewhere like Guy's that has, you know, such a large number of patients" "when you roll it out it's going to be a very big scale number of patients" "You know we're struggling, I say as a team you know within all of the services there is a struggle with the amount of patients coming through the door per clinic for people to be seen in a timely manner"
Inner Setting domain - Recipient-Centeredness	Routine PROM collection may impact the relationship between patients and their healthcare providers	"PROM data could be used to...improve that sort of clinician patient shared communication decision making process" "So sometimes we use it, just to have a conversation with the patient and we also use it for patient education purposes" "I think they all recognise the benefit of getting the patients to tell us themselves how they're feeling" "I think it's to actually check in with a patient in a more kind of substantive way not make assumptions about where a patient's at"

Inner Setting domain - Work Infrastructure	• It is perceived that the implementation will result in an increase in workload of clinical teams • There are issues with recruitment and retention of staff	"Introducing PROMs is not going to reduce workload. It's gonna increase work it, it's potentially going to increase workload" "I think as soon as clinicians get the feeling that this is creating more work, then engagement drops" "a fundamental barrier as far as I'm concerned is, is recruitment and retention" "We have a huge staff shortages at the moment. It's not just recruitment, there isn't anybody out there to recruit"
Inner Setting domain - Access to Knowledge & Information	• Healthcare professionals lack knowledge on how to implement and/or utilise PROMs: i) Training and counselling on PROMs and implementation process ii) Training and counselling on use of electronic PROMs platform iii) Lack of available data on how to interpret PROM scores iv) Lack of available data on how to use PROM scores in routine clinical practice	"So I think some general education to start with and understanding what a PROM is yeah, what a PROM is would be the starting point" "But the bit that I think is lacking at the moment is a general education of the use of PROMs" "I think whoever does the role needs to be trained, not just about what you're looking at on the form, but also to, you know, be able to analyse the results, to be able to highlight it" "simple education and how to use the interface" "I think graphical presentation is often easier to interpret obviously having a a score is also helpful" "if there was somebody that was going to be able to help analyse the data like the trigger points, then some kind of training would certainly be involved"

		"And a little bit of training, they don't need to know all the clinical data, but I certainly think it would be useful"
Inner Setting domain - Available Resources	• It is necessary to free up other clinical time to facilitate routine PROM collection • There is a lack of dedicated follow-up clinics to refer patients onto • Lack of resource available to ensure compliance across each follow-up timepoint • Potential risk associated with use of an eplatform to collate and/or store sensitive data • An eplatform which is user-friendly needs to be implemented • There is no bespoke method for presenting PROM data on the implemented eplatform	"one of the key challenges with PROMs is that we'll have a whole sort of lot of patients with problems that have been highlighted but we won't necessarily know how to tackle those problems" "I think in general we need more late effects clinics and things like that and to manage, because for a patient, you know, if we collect them and they can write that they have terrible sexual dysfunction but if there's nothing we can do about it and nothing we can offer them, then you know, it's quite frustrating for both parties" "I think you get more compliance if the patient's actually met you, or spoken to you on the phone and then it's the same person reviewing them, then you get that trust don't you, and that compliance" "I think one thing is going to be compliance, we're going to the patients to

		complete it and I can't say at this stage, they've all agreed to it, they're all going to actually send those questionnaires back, and send them back in a timely manner" "A presentation on that would be ideal too, just to gather some data together and yeah and actually show it and demonstrate how easy it can be once the system is built" "it would be nice to obviously see their current responses and previous responses to see if there is a trend towards changes and specific sort of problems developing"
Inner Setting domain - Space	• There is a lack of physical space available in the clinical settings to administer PROMs	"So, but you know, space is going to be an issue because Tuesday is chockablock. There is no room for the person to have" "for the PRUH I think space is going to be an issue because there are only a limited number of clinic rooms"
Inner Setting domain - Information Technology Infrastructure	• Implemented PROM eplatforms are unable to be integrated with electronic health records	"And as I said before, ideally it should be integrated into our electronic note system" "I think the infrastructure exists, I think a big barrier to that is various systems talking to one another"

Inner Setting domain - Funding	• There is a lack of funds available to support routine PROM collection and implementation process	"some clinic teams would have preclinic meetings where we would go through patients and sort of review where they are at...and so senior management have said that that time will no longer be paid for" "Maybe financial if you're, you know, wanting to send them to the patients because then, you know, they're gonna get them. And then again financial because you could have somebody that would call them up to ensure that they do it and send it back"

A variety of barriers were identified within the inner setting domain of the CFIR. Firstly, stakeholders identified that a lack of available funds may impede the implementation process as well as the scale-up and sustainability of the programme. One healthcare professional explained that, previously, preclinical meetings would occur to review results and discuss patients but that, owing to NHS financial pressures, such meetings would no longer be funded. Termination of such scheduled meetings could impact the implementation as these meetings would provide a setting for discussing the PROM scores of patients. Equally, a lack of funds would have implications for the implementation process in terms of the collection of PROMs including the logistics around administration and coordination of sending the questionnaires.

Furthermore, interview participants identified the lack of integration of both REDCap and DrDoctor with the electronic health record platforms as a barrier. One healthcare professional noted "I think the infrastructure exists; I think a big barrier to that is various systems talking to one another". Although REDCap includes functionality to facilitate clinical interoperability with electronic health record systems, it was not possible to get this implemented as part of the PROM collection feasibility study because of the pressures faced by IT departments in the rollout of EPIC.

Moreover, a further identified barrier in this implementation process was the availability of physical space to administer PROMs. One clinician observed, "so you know, space is going to be an issue because Tuesday (clinic) is chock-a-block. There is no room for the person to have". In addition, another participant remarked "for the PRUH (Princess Royal University Hospital) I think space is going to be an issue because there are only a limited number of clinic rooms".

Another important inner setting barrier identified in this study was a lack of dedicated follow-up clinics to refer patients onto. Two participants independently stated “one of the key challenges with PROMs is that we’ll have a whole sort of, lot of patients with problems that have been highlighted but we won’t necessarily know how to tackle those problems” and, “I think in general we need more late effects clinics and things like that and to manage, because, for a patient, you know, if we collect them and they can write that they have terrible sexual dysfunction but if there’s nothing we can do about it and nothing we can offer them, then you know, it’s quite frustrating for both parties”.

In addition, interviewees observed that patient compliance with PROM completion may pose a further barrier to the implementation process. A participant noted, “I think one thing is going to be compliance, we’re going to the patients to complete it and I can’t say at this stage, they’ve all agreed to it, they’re all going to actually send those questionnaires back, and send them back in a timely manner”.

The interview study also elucidated that healthcare professionals may lack knowledge on how to implement and utilise PROMs, and this was deemed another important barrier in the implementation process. One participant stated, “But the bit that I think is lacking at the moment is a general education of the use of PROMs”. Additionally, the interview study highlighted a further barrier related to the recruitment and retention of staff at Guy’s Cancer Centre. Two seminal quotes which emerged included, “a fundamental barrier as far as I’m concerned is, is recruitment and retention” and, “we have huge staff shortages at the moment. It’s not just recruitment, there isn’t anybody out there to recruit”. Finally, the increasing patient numbers attending the Trust was deemed a barrier impacting implementation success. One interviewee observed, “you know, we’re struggling, I say as a team, you know, within all of the services with the amount of patients coming through the door per clinic for people to be seen in a timely manner”.

6.1.3.2.4 Individuals

Table 37: Individuals domain barriers and facilitators to implementation of routine clinical PROM collection at Guy's Cancer Centre

CFIR domain	Barriers and facilitators to implementation	Seminal quote(s)
Individuals domain - Innovation Recipients	• Proportion of patients are digitally illiterate • Health inequality: certain demographics of patients experience difficulties with completing PROMs: i) lack of understanding of cancer diagnosis, care and impact of PROMs ii) lack of understanding of PROM language and/or response options and scales • Patient disability impacting ability to complete PROMs • Patient burden: i) time required to complete PROMs (time at each event and how regularly administered) ii) PROMs as an addition to clinical appointments, procedures, tests • Information burden (patients inundated with vast amounts of	"there's language barriers, people who might be hard of hearing, or struggle to access the technology, or don't have any of that support at home yeah I guess issues around reading and that kind of thing" "then I think that we will have a problem especially in our area with the demographic that we have, with some patients not having access to um to tablets etcetera to complete them" "Most of our patients come with family members or relatives that on the whole do most of the talking in the consultations actually, that happens quite a lot, because our patients usually have short term memory impairment and sometimes don't have insight into some of the issues that they have" "You know that we we inundate them with information time after time. So I think that could that could have an implication on take up"

	information as part of care)	
Individuals domain - Need	PROMs can be used to address unmet need(s) of patients	"it's becoming a kind of chronic illness, that a lot of the treatments that we use are going to have..as people are surviving longer and have longer term side effects.. that need to be addressed" "we're not very good at picking them up...we're not really sort of skilled in knowing how to manage that late effect" "I've spoken personally to to colleagues, but also to to friends and family who I know have gone through a cancer diagnosis and have often felt that their needs are unmet following their treatment" "it's just triaging patients in a more effective manner and making sure they get the appropriate support in the appropriate time" "understand you know the how it's affecting

		the patients quality of life and then to be able to highlight to somebody to manage that you know if LUTS has gone up significantly and the quality of life score has gone up then they they should know to to highlight it"
Individuals domain - Capability	• Lack of patient understanding: i) patient understanding on what a PROM is ii) patient understanding of PROM content	"Absolutely yes in terms of education. Because you know, what you don't want is for them to just tick boxes and not be sure about what they are actually ticking" "I think maybe if we could you know, have some written information for patients or umm, you know a a link that would go out or the text message when they're invited to clinic" "So patient information is pretty pivotal in education"

Individuals domain - Motivation	• Lack of patient understanding on the value and impact of completing PROMs • Lack of patient motivation to complete PROMs	"a lot of these patients are not motivated to be honest" "I think you just kind of need to just explain why we're collecting it but again we could just put a movie on in the cancer centre" "making sure the patients kind of take it on board if there's lots of stuff going on at the same time, making sure they actually really understand what it's for, how often and that they go away with something that reminds them of that and that they know how to use the system, they feel confident that something will happen as a result of it"
Individuals domain - Innovation Deliverers	• Buy-in needs to be ensured from all relevant stakeholders to enable routine PROM collection • Roles need to be defined to enable routine clinical PROM collection • Administrative support is required to undertake logistics of PROM collection • There is a high turnover of staffing in administrative roles at Guy's Cancer • Technical support is required to build and maintain electronic PROM platforms	"I don't think people have been engaged with PROMs that much either. Using them, developing them, understanding how they're meant to be used" "We have a huge staff shortages at the moment" "we don't have enough specialists in the hospital to actually manage them" "We're trying to get more members in the team and if we did then that's another something or other that they could do" "I would have thought that we would need an admin person for that role, and that person would be able to help relieve some of the sort of clinic prep" "but you know, somebody that is solely in charge of this. So it is their responsibility to do because then they will need to do it. Umm so the right person" "And somebody, you know, that's going to manage the data."

Within the individuals' domain, one observed implementation barrier referred to the digital illiteracy of a proportion of the population served by Guy's Cancer Centre. Equally, it was noted that there exists health inequality and some patients may experience difficulties in terms of completing PROMs. One healthcare professional explained, "then I think that we will have a problem especially in our area with the demographic that we have, with some patients not having access to um, to tablets etcetera to complete them". A further seminal quote observing the health inequality of the patient population was "there's language barriers, people who might be hard of hearing, or struggle to access the technology, or don't have any of that support at home yeah I guess issues around reading and that kind of thing". Moreover, an additional barrier related to patient information burden as patients are inundated with vast amounts of information as part of standard of care. One participant stated, "You know, that we, we inundate them with information time after time. So, I think that could, that could have an implication on take-up".

Moreover, a number of the interview participants felt that lack of patient understanding of PROMs may be a barrier in the implementation process. Furthermore, emerging barriers referred to a lack of patient understanding on the value and impact of completing PROMs, coupled with a lack of patient motivation. One of the interviewees explained, "a lot of these patients are not motivated to be honest".

Finally, the interview study emphasised that administrative support would be required to undertake the logistics of PROM collection. However, it was determined that there is a high turnover of staffing in administrative roles at Guy's Cancer; "we have huge staff shortages at the moment", and "we're trying to get more members in the team and if we did then that's another something or other that they could do". Additionally, buy-in is required from all relevant stakeholders to ensure the success of the implementation process, and this was deemed to be a barrier. One clinician observed, "I don't think people have been engaged with PROMs that much either. Using them, developing them, understanding how they're meant to be used".

6.1.3.2.5 Implementation process

Table 38: Implementation process domain barriers and facilitators to implementation of routine clinical PROM collection at Guy's Cancer Centre

CFIR domain	Barriers and facilitators to implementation	Seminal quote(s)
Implementation Process domain - Engaging	• Staff need to be engaged to demonstrate the clinical value of routine PROM collection	"that they would understand the importance of the metrics that we would, we would gather at the same time of how we could improve our service, so knowing that they were delivering the best patient care and that we can measure that and demonstrate it, maybe a very good incentive" "Anybody that encounters patients during their pathway would need to be engaged with it" "also for staff so that they understand exactly what the purpose is and and understand why"
Implementation Process domain - Assessing Needs	• Prior to implementation, consensus needs to be reached on: i) which PROMs to collect across multidisciplinary teams (acknowledging PROM validity, relevance, burden, content, and comprehensibility) ii) when to collect PROMs (proposed frequency, alignment with clinical schedule, length of follow-up)	"it's sitting down right with all the clinicians. What tool do you want to use? You know what this, what that" "probably one of the most difficult things to to agree on how frequently they should be collected"

	iii) "sweet spot" to administer PROMs to optimise compliance	

A couple of barriers relevant to the implementation process domain emerged during the interview study. The first related to the need for consensus to be reached on which PROMs to administer at which timepoints, to facilitate successful implementation. One stakeholder acknowledged, "it's sitting, right, with all the clinicians. What tool do you want to use? You know, what this, what that", whilst another remarked "probably one of the most difficult things to, to agree on how frequently they should be administered".

Equally, the necessity of staff engagement was also highlighted as a critical factor in ensuring implementation success. One interviewee observed that, for implementation of routine PROM collection to be successful, "anybody that encounters patients during their pathway would need to be engaged with it".

6.1.4 Discussion

Overall, this evaluative interview study sought to identify a comprehensive list of barriers and facilitators influencing the implementation of routine clinical PROM collection, through engagement of key stakeholders at Guy's Cancer Centre. Such engagement of stakeholders is viewed as an essential component of implementing complex interventions, as co-learning exercises that address contextual factors can result in more effective intervention implementation.

Data from the inner setting supported the value of accounting for access to knowledge and information and focused on the available resources impeding implementation within the Trust including physical space, information technology infrastructure, and funding. In terms of the outer setting, data suggested that local conditions, performance measurement pressure, and external pressure such as the competing time demands of clinical staff, were key barriers influencing the implementation process. Additionally, within the individual's domain, the capability, motivation, and needs of the patients emerged as contextual factors influencing implementation, as well as the engagement, support, and input of innovation deliverers. Finally, the necessity of gaining consensus when designing the intervention, as well as ensuring the adaptability of the programme, arose as further barriers impacting routine clinical PROM collection at Guy's Cancer.

Emerging CFIR-ERIC implementation strategies, selected to overcome identified barriers, are presented in Table 39 prior to comprehensive discussion below.

Table 39: CFIR-ERIC implementation strategies identified to address the implementation barriers which were elucidated through qualitative evaluation of the feasibility study.

Implementation barrier	Identified implementation strategy (CFIR-ERIC)
• The clinical teams implementing the routine collection of PROMs have many competing time demands • It is perceived that the implementation will result in an increase in workload of clinical teams • It is necessary to free up other clinical time to facilitate routine PROM collection • Roles need to be defined to enable routine clinical PROM collection • Administrative support is required to undertake logistics of PROM collection	Create new clinical teams
• Staff need to be engaged to demonstrate the clinical value of routine PROM collection • Healthcare professionals lack knowledge on how to implement and/or utilise PROMs	Develop educational material Disseminate educational material
• There is a high turnover of staffing in administrative roles at Guy's Cancer	Conduct ongoing training
• Roles need to be defined to enable routine clinical PROM collection	Make training dynamic
• There is a physical space available in the clinical settings to administer PROMs • Lack of patient understanding on the value and impact of completing PROMs • Administrative support is required to undertake logistics of PROM collection • Health inequality: certain demographics of patients experience difficulties with completing PROMs	Change physical structure and equipment
• Proportion of patients are digitally illiterate • Health inequality: certain demographics of patients experience difficulties with completing PROMs	Conduct local needs assessment
• Implemented PROM eplatforms are unable to be integrated with electronic health records • It is unclear what the impact of roll out of the new electronic health record platform will be on routine PROM collection	Use data warehousing techniques Facilitate relay of clinical data to providers Use data experts Provide local technical assistance Conduct ongoing training

• Lack of patient motivation to complete PROMs • Patient disability impacting ability to complete PROMs • Lack of patient understanding of PROMs and PROM content	Involve patients/consumers and family members
• The implementation process will need to be adapted to enable scale-up across Guy's Cancer	Audit and provide feedback Identify and prepare champions Capture and share local knowledge
• There is a lack of funds available to support routine PROM collection and implementation process	Identify and access new funding

Overall, data from the interviews suggest the necessity of introducing dedicated roles within the clinical setting to facilitate the implementation and sustainment of routine PROM collection. Such resources were highlighted as an integral component at all levels of the feasibility study, from engagement of patients to the collection and interpretation of the PROM(s) at each of the dedicated timepoints. The undertaking of the feasibility study relied on the availability of radiographers to facilitate PROM collection, however this staffing group faced increasing clinical burden and reduced availability of time over the duration of follow-up. The creation of new clinical teams therefore emerged as the first implementation strategy, and various interview participants suggested that administrative staff may be able to take on such roles.

The next identified implementation strategy was closely linked to the creation of new clinical teams. The importance of developing educational materials for stakeholders delivering the routine collection of PROMs emerged as a key strategy to facilitate success of this programme. It was suggested that such educational materials could take the form of online training courses developed to highlight the value of PROMs, whilst also explaining how such questionnaires can be interpreted and utilised within clinical settings. Also emerging was the importance of conducting ongoing training and making any training provisions dynamic. Interview data highlighted that the high turnover of staff was a key barrier impeding implementation and participants noted that continued advocacy of the value of routine clinical PROM collection may be necessitated to ensure success. Additionally, differing methods to administer training may need to be employed in order to cater to the various roles involved in delivering the PROM collection innovation.

A lack of available infrastructure, in terms of physical space, interoperable IT settings, and dedicated follow-up clinics also became evident as independent barriers affecting the feasibility study. Several interview participants highlighted that there was no additional space, in terms of clinic rooms, available to facilitate the collection of PROMs within the busy clinical setting. This was salient, as

additional identified barriers related to the necessity of on-going patient counselling and provision of pen and paper PROM administration to address the existing health inequalities seen across the hospital catchment. Changing the physical structure of the clinical setting and equipment available was proposed as a possible implementation strategy: for patients requiring further assistance it was suggested that the PROM questionnaires could be administered within a dedicated area of the waiting room using iPads, and that administrative staff could be on hand to provide counselling to such a cohort of patients. Conducting a local needs assessment could be utilised to determine the proportions of patients per tumour type requiring such additional input and to ensure the necessary infrastructure provisions were implemented for scale-up.

Moreover, interview data suggested that the lack of dedicated follow-up clinics was a critical barrier impeding the success of the routine clinical collection of PROMs. A number of interview participants voiced their concerns around the dangers of collecting symptom data related to disease which then cannot be addressed by the clinical teams, i.e., collecting PROMs for the sake of collecting PROMs. It was suggested that the development of new clinical pathways and processes may assist in overcoming such a barrier; for example, putting in place the necessary infrastructure to refer prostate cancer patients suffering erectile dysfunction to the erectile dysfunction clinic, and ensuring that such clinics have enough resource available to support any increased demand.

Equally, the impact of the roll-out of the new centralised IT platform (EPIC) across Guy's and St Thomas' NHS Foundation Trust was raised as a barrier in the sustainment of this feasibility study. During the feasibility study, the REDCap platform was utilised to facilitate electronic collection of PROMs (through automated survey invitations) and as a data repository to store data. Owing to the scheduled go-live of the EPIC platform in April 2023, the local IT departments were not willing to prioritise adoption of the clinical interoperability features of REDCap and integration with the existing electronic health record platforms of the Trust. This meant that no automated feed of data between platforms was achievable, which was noted as an infrastructural barrier in this study. The use of data warehousing techniques was therefore identified as a possible future implementation strategy where EPIC would replace REDCap as the sole PROM collection platform. The use of one electronic health record platform alone would, in turn, centralise all patient related data and alleviate clinician burden in terms of access to multiple systems during clinical consultations.

Prior to the go-live of EPIC, a number of interim implementations strategies were identified to ensure the success of implementation using the REDCap platform. These strategies were based around the ERIC domain of facilitating the relay of clinical data to providers whereby real-time data about key measures is provided to stakeholders using integrated communication channels. To

overcome the barrier of lack of integration with existing clinical record platforms, it was suggested that traffic light monitoring dashboards and easily interpretable graphs could be developed within REDCap to provide the clinical teams with an overview of each patient's PROM scores, within the platform itself. In order to facilitate this, further implementation strategies of "use data experts" and "provide local technical assistance" were suggested to provide the technical support to develop and manage this. Additionally, on-going training and the provision of educational materials on the use of REDCap was recommended to ensure that all members of the clinical team would feel confident knowing how and where to access the data collated from the PROMs.

Furthermore, barriers related to patient motivation and their capability to complete PROMs consistently emerged throughout the interview study. One identified implementation strategy, which arose during the subsequent exploratory focus group with patients, focused on the obtaining and use of patients and their family's feedback. The importance of involving patient representatives and consumer panels throughout the process of implementation, from the initial selection of PROM instruments through to the interpretation and use of the PROMs, was highlighted as an integral component impacting programme success and sustainment. An identified strategy involved the development of educational materials, with input from patient representatives and consumer panels, which could be disseminated to patients at regular intervals throughout their cancer journey.

In addition, throughout this qualitative interview study, barriers related to the adaptability of the implementation process depending on context, and the on-going performance measuring pressure were consistently identified. The feasibility study was undertaken in a small subset of prostate cancer patients undergoing radiotherapy and it was assumed that processes would need to be amended to ensure success upon scale-up both within and across tumour types. The first identified implementation strategy referred to the process of auditing and providing feedback on clinical performance data over set periods of time to monitor, evaluate and modify provider behaviour. To facilitate this auditing process, it was suggested that champions should be identified to dedicate time in support of the implementation and facilitate dissemination of the results of auditing to the relevant clinical teams to overcome resistance. Additionally, to promote the adaptability of the PROMs implementation programme an evolving implementation strategy refers to the capturing and sharing of local knowledge. In the setting of this feasibility study, local knowledge and key learnings from the prostate radiotherapy setting could be shared across other sites and tumour groups to promote success in such alternate settings.

Finally, funding, or the lack of an allocated funding resource, was the most prominent barrier identified throughout this qualitative interview study. Indeed, funding resource underpinned several

of the barriers emerging within this study such as lack of staffing resource to undertake the operational aspects of the feasibility study and the provision of technical support, limited choice in terms of freely available database infrastructure, lack of NHS funding in terms of making PROM collection a clinical priority, and availability of clinical and physical infrastructure to support the necessary clinical management of patients completing PROMs. The feasibility study was undertaken without dedicated funding resource and highlighted the need to identify and access new funding to ensure implementation sustainment. In terms of alternate implementation strategies, an economic evaluation of the financial impact of the implementation was suggested to provide insight into the risks and benefits of the programme. Such an evaluation could be utilised to weigh up the costs of implementing the routine clinical collection of PROMs versus any potential monetary savings arising from early intervention, where patient symptom burden, which otherwise may not have been managed, is identified using PROMs. Early intervention is economically preferable in the prevention of longer-term chronic side effects of disease and its associated treatment.

6.1.4.1 Strengths and limitations

Overall, this qualitative study of fourteen semi-structured interviews met evidence-based guidelines for sample size and involved a diverse range of healthcare professional roles located across the various sites of Guy's Cancer Centre (435). The results are therefore generalisable across the sites of Guy's and St Thomas' NHS Foundation Trust but may not be applicable to alternate NHS sites of similar size and scope. The participants of the interviews were also selected using selective sampling, and the results may therefore not represent the views of other healthcare professionals who did not participate.

The use of qualitative methods in feasibility study evaluation is increasing in the literature but, to our knowledge, this is the first study undertaken in the context of routine clinical PROM collection in NHS cancer settings. It was possible to gather unique insights using this methodology which resulted in robust assessment of the contextual factors impacting PROM implementation. Additionally, perceptions on strategies to overcome such implementation barriers can be accepted as credible and dependable owing to the variety of participants involved in this process.

6.1.5 Conclusions

This study with healthcare professionals employed by Guy's Cancer Centre yielded important data regarding the barriers and facilitators impacting the routine clinical collection of PROMs within the cancer setting of this site. Additionally, the study facilitated the commencement of identification of implementation strategies to support the improvement of the programme, as well as the scale-up and sustainment of implementation. The findings suggest that there exists a number of contextual

factors impeding successful routine clinical PROM collection across the five domains of the CFIR. Initial findings also support the use of implementation strategies related to training and education, acquisition of funding, technical and clinical team championing, and adaptability of the programme to improve the implementation and sustained use of PROMs clinically in NHS settings.

6.2 Quantitative feasibility study evaluation

6.2.1 Rationale

As described in Chapter 6.1, the Consolidated Framework for Implementation Research (CFIR) comprises a comprehensive taxonomy of factors which influence the implementation of complex interventions. The CFIR was previously applied in Chapter 6.1 to guide the development and analysis of a qualitative evaluation of the feasibility study described in Chapter V. In the study outlined in Chapter 6.1, semi-structured interviews were conducted with healthcare professionals identified as key stakeholders at Guy's Cancer Centre, to determine contextual factors and determinants impacting the success of the PROMs feasibility study.

Further to the previously described qualitative evaluation, an additional implementation framework was selected for application in this thesis to facilitate the continued advancement of the implementation process. Specifically, Proctor's Implementation Outcomes framework (IOF) was adapted to develop corresponding feasibility study implementation outcomes assessing the internal and external validity of the programme. The IOF was selected for this purpose as the CFIR represents a determinant framework which does not explicitly incorporate implementation outcomes.

As described by Kirk et al, the assessment of implementation outcomes is critical in the field of implementation science as optimal implementation outcomes are necessary to ensure innovation effectiveness (436). Additionally, the measurement of implementation outcomes can be utilised as a tool to advance the understanding of implementation processes, and enhance efficiency in implementation research (437). Despite compelling evidence to support the assessment of implementation outcomes, a recent systematic review of studies applying the CFIR identified that less than half of the included studies reported investigation of implementation outcomes (436). This represents a significant gap in the literature which can be addressed using measures of implementation effectiveness, as conceptualised in Proctor's framework of implementation outcomes.

As illustrated in the IOF, implementation outcomes precede and are distinct from service and client outcomes. Proctor defined implementation outcomes as the effects of deliberate and purposive actions to implement new treatments, practices, and services, and implementation outcomes primarily serve as indicators of implementation success. Ultimately, interventions will not be effective if not implemented well, and implementation outcomes are an essential prerequisite for accomplishing improvements in service and client outcomes. Various examples of the differing types of outcomes included within the scope of implementation, service and client outcomes are presented below in Figure 9.

9. Figure 9: Examples of types of outcomes utilised in implementation research, as adapted from Proctor's original manuscript entitled *Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda* (437).



Proctor's framework of Implementation Outcomes is formed of a heuristic taxonomy of eight conceptually distinct outcomes of implementation: termed as acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability. Definitions of each outcome are provided below:

Acceptability: the perception amongst implementation stakeholders that a service or innovation is agreeable, palatable, or satisfactory (437).

Adoption: Proctor's definition of adoption aligns with definitions provided by Rabin et al and Rye and Kimberly; it is defined as the intention or action to employ an evidence-based practice (438, 439). Adoption is usually assessed by the practice provider(s) and can also be referred to as "uptake".

Appropriateness: appropriateness is largely classified as the relevance or compatibility of the innovation or evidence-based practice for a given setting, provider, or consumer (437). Appropriateness also refers to the perceived fit of an innovation or practice to address a particular issue.

Cost: refers to the overall costs associated with an implementation endeavour (437).

Feasibility: feasibility is described as the extent to which an innovation or evidence-based practice can be successfully used or undertaken in a specific setting(s) (440).

Fidelity: fidelity refers to the degree to which a practice was implemented as initially intended (441).

Penetration: the integration or embedding of an implemented practice within the service setting and subsystems (442).

Sustainability: defined as the extent to which a newly implemented innovation or practice is maintained, institutionalised, or normalised within a service's on-going practices (438, 443, 444).

Overall, this study aimed to quantitatively assess the implementation effectiveness of the feasibility study described in Chapter V, through employment of Proctor's framework of implementation outcomes. Various of the conceptualised implementation outcomes were addressed independently utilising two methods: (1) development of a survey which was administered to the patients recruited to the feasibility study, and (2) provider appraisal of the feasibility study.

6.2.2 Methods

6.2.2.1 Evaluative questionnaire

6.2.2.1.1 Development of an evaluative questionnaire

Firstly, a questionnaire was developed to gain insight into the experiences of the patients recruited to the feasibility study of routine clinical PROM collection. Implementation outcomes which were relevant specifically to the recruited patients were therefore selected for assessment using the developed questionnaire. Overall, different aspects of acceptability, appropriateness and feasibility were assessed from the patient perspective in this study.

The Grid-Enabled Measures Database (GEM) was utilised as a tool to guide questionnaire development. GEM is a National Cancer Institute (NCI) web-based repository of measures relevant to behavioural, social, and other types of scientific research, which aims to support collaborative research and efficient science through the reuse of measures existing in the literature (445). The GEM database was searched by construct (e.g., acceptability, appropriateness, and feasibility) to identify associated validated questionnaires and measures, where available. The questions of this evaluative questionnaire were subsequently developed, as informed by these previously published measures. Once drafted, the evaluative questionnaire was reviewed by prostate cancer patients involved in the Patient Public Involvement and Engagement (PPIE) activities of Guy's and St Thomas' NHS Foundation Trust, and further iterations were developed based on their feedback on content and language. The finalised version of the questionnaire is included as Appendix IX.

6.2.2.1.2 Participants and questionnaire distribution

The questionnaire was distributed to feasibility study participants utilising two methods: patients who had opted to complete the EPIC-26 questionnaire electronically utilised the REDCap platform to complete the evaluation questionnaire, and patients who opted for paper completion received it via post complete with a stamped return envelope. The questionnaire was distributed to the feasibility study participants between July 2022-October 2022 in line with the 1-year follow-up timepoint of the study.

6.2.2.1.3 Data handling and analysis

Questionnaire responses were entered onto the REDCap platform directly by the participant themselves, or by myself once postal responses were returned. Following closure of the study in November 2022, all returned data was exported from the REDCap platform in anonymised format and stored securely on a Guy's and St Thomas' NHS Foundation Trust computer. Patients' postcodes were used to generate Indices of Multiple Deprivation as a measure of socioeconomic status. Data was analysed in a descriptive manner, using Microsoft Excel.

6.2.2.2 Provider assessment

In this study, adoption of the feasibility study was evaluated from the provider perspective. The uptake of patients at each follow-up timepoint was assessed at the patient and population level in terms of compliance to the implementation schedule of completion of the EPIC-26 questionnaire. Compliance at each time point was presented per patient and overall compliance rates calculated at the population level. Additionally, compliance was observed based on the characteristics of the population. Compliance at each timepoint was tabulated according to the ethnicity, socioeconomic status, and age of the feasibility study population.

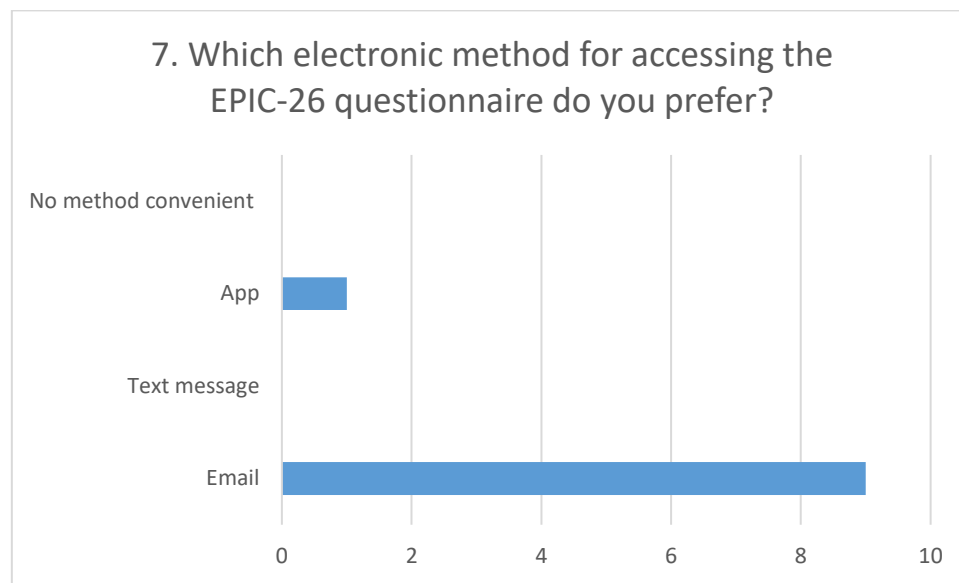
6.2.3 Results

6.2.3.1 Evaluative questionnaire

In summary, 10 prostate cancer patients successfully completed the evaluative questionnaire (representing 50% of the total feasibility study population). Of the ten respondents, nine were completing the EPIC-26 questionnaires electronically through automated email invitations and one was completing the PROM at each timepoint using pen and paper.

The majority of the patients indicated that, for electronic completion of PROMs, an email link was the most convenient method of receiving the quality-of-life measures (Figure 10). Interestingly, no patient specified a preference for completing PROMs using a mobile phone, and only one mentioned that a downloadable app would be their preferred mode of electronic administration.

10. Figure 10: Figure presenting the preferences of feasibility study participants, in terms of the electronic methods available to complete patient-reported outcome measures.



Of the patients completing the PROMs electronically ($n = 9$), 78% of patients thought it was very easy to access the REDCap platform from the email link (22% indicated it was fairly easy), and 67% of patients thought that REDCap was easy to navigate in terms of completing the questionnaire.

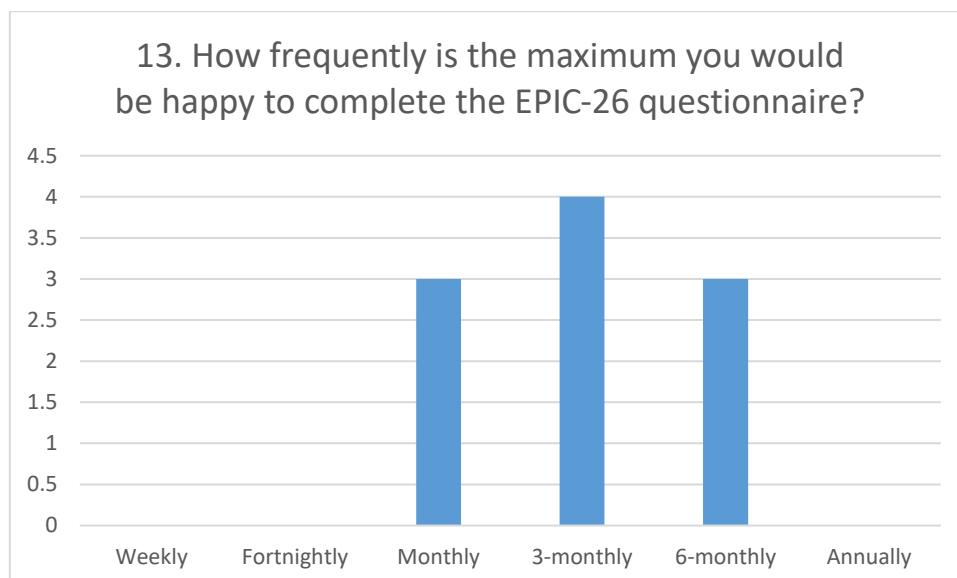
Participants were asked whether they would know who to contact if they experienced any difficulties completing the questionnaire (in terms of mode of administration or PROM content and language) and 70% of the patients indicated that they would not know where to find help. Despite this, 90% of the population thought that the questions of the EPIC-26 PROM were very or reasonably easy to understand and no patient reported any difficulty with completion at any timepoint.

On average, patients reported that the completion time of the EPIC-26 PROM was 15 minutes (S.D. 11.5 minutes) however the completion time responses ranged from 5 minutes – 45 minutes. When the one outlier of 45 minutes was removed, the average completion time reduced to 11.25 minutes (S.D. 4.85 minutes). Overall, 90% of the participants indicated that the time taken to complete the EPIC-26 questionnaire was very or reasonably acceptable. The patient who indicated an average completion time of 45 minutes scored this question neutrally (neither acceptable nor unacceptable).

In terms of the follow-up schedule which was developed for this feasibility study (EPIC-26 administered just prior to radiotherapy treatment, and then at 6-weeks, 3-months, 6-months, 12-months, 18-months, and 24-months post end of treatment), 40% of patients thought that the schedule was just right but 60% specified that, in their view, the PROMs were not administered frequently enough. Despite this, only three patients opted for a follow-up schedule of monthly administration of the EPIC-26 PROM. Four patients indicated that 3-monthly administration would

be the maximum acceptable time period between PROMs, and three patients noted that 6-monthly administration would be preferable.

11. Figure 11: Figure outlining the maximum frequency of PROM administration which was acceptable to feasibility study participants.

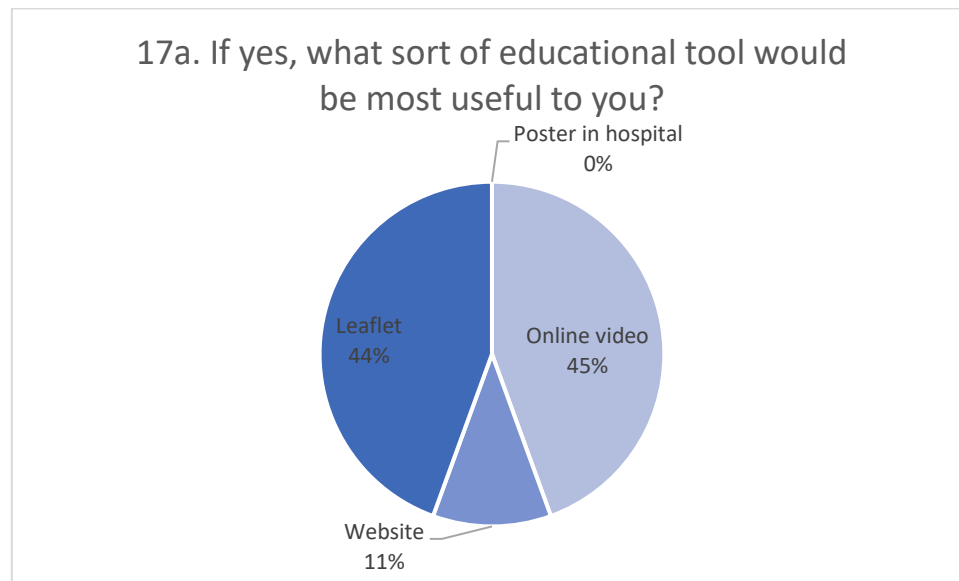


The vast majority of the patients observed that they had completed the EPIC-26 PROM fully at each timepoint; one patient experienced an issue with their mobile phone which prevented full completion of the PROM at one timepoint, and another mentioned some comments around the crude nature of the sexual functioning questions which meant that he did not fully complete the PROM at each timepoint.

Of the ten patients, seven could remember receiving information about the EPIC-26 questionnaire (including what a PROM is and its value) from the clinical team. In line with the day-to-day undertaking of the feasibility study, the majority of patients indicated that a nurse or radiographer had provided this information. Additionally, some patients noted that they had received counselling from a researcher or their treating consultant.

In total, 88.9% of responding participants thought that an educational tool would be useful to explain PROMs and their role in the routine clinical setting. 45% of patients specified that an online video format would be the most useful educational tool and 44% preferred a printed leaflet for this purpose. Additionally, 11% of the patients felt that a dedicated website or webpage could be useful for providing education on PROMs.

12. Figure 12: Pie chart describing the format of patient educational tool which was highlighted as most preferable to feasibility study participants.



Finally, one third of the respondents believed that the EPIC-26 questionnaire had been a useful method for describing their symptoms and quality of life after radiotherapy treatment.

Contrastingly, 11.1% indicated that the EPIC-26 instrument was not useful for describing such functioning and symptomology. Two patients felt that their involvement in the feasibility study had improved their care but four responded that no changes to their care had been observed. Despite this, 77% of patients specified that they would be very likely or likely to complete further PROMs related to their cancer care.

6.2.3.2 Provider assessment

6.2.3.2.1 Adoption

Firstly, the compliance rates of the 20 prostate cancer patients were reviewed at each follow-up timepoint. Table 40 illustrates each patient's completion of the EPIC-26 questionnaire across the follow-up journey: the table was created in January 2023 with green squares representing completion of the PROM, red indicating non-compliance at that timepoint, and grey signifying patients that had yet not reached that timepoint in the schedule, at the point of table creation.

Table 40: Table presenting the compliance of each patient recruited to the feasibility study, at each scheduled follow-up. Note: green is used to indicate completion of the EPIC-26 PROM as expected, red represents non-completion, and grey was utilised where patients had not yet reached that timepoint of follow-up at the point of compliance assessment.

	Mode of Administration	Baseline	6-week	3-month	6-month	1-year	18-month
Record 1	Electronic						
Record 2	Electronic						
Record 3	Postal						
Record 4	Electronic						
Record 5	Electronic						
Record 6	Postal						
Record 7	Electronic						
Record 8	Electronic						
Record 9	Electronic						
Record 10	Electronic						
Record 11	Electronic						
Record 12	Postal						
Record 13	Electronic						
Record 14	Postal						
Record 15	Postal						
Record 16	Electronic						
Record 17	Electronic						
Record 18	Electronic						
Record 19	Electronic						
Record 20	Electronic						

Population-level compliance rates at each timepoint were subsequently calculated and are presented in percentage format: across each timepoint (up to 1-year follow-up) the average compliance rate was 59%. Interestingly, the compliance rates appeared to improve throughout the feasibility study duration. At 6-weeks and 3-months the compliance rates were 55%, i.e., 11 of the patients completed the EPIC-26 questionnaire as expected. Compliance rates then improved at the 6-month and 1-year timepoints and were calculated as 65% compliance at 6-months and 61% at 1-year.

When observing the compliance rates at the individual patient level, it was noted that non-compliance could largely be attributed to a proportion of patients who remained non-compliant throughout the duration of the feasibility study. Specifically, records 2, 4, 10, and 20 did not complete any of the EPIC-26 questionnaires after the baseline timepoint. Additionally, records 14, 15 and 19 each only successfully completed one follow-up PROM, at the 6-week and 6-months

timepoints, respectively. In contrast, six of the recruited patients (30%) successfully completed all questionnaires as expected, at each follow-up time point.

Compliance with questionnaire completion at each timepoint was then observed according to the characteristics of the population. At each timepoint, compliance vs noncompliance was described based on the ethnicity, socioeconomic status, and age categories of the prostate cancer patients. This data is presented in Tables 41-43.

Table 41: Compliance vs noncompliance at each timepoint of follow-up based on the ethnicity of the patient population.

Ethnicity		Black (n(%))	Mixed (n(%))	White (n(%))
Baseline				
	Non-compliant	0 (0.0)	0 (0.0)	0 (0.0)
	Compliant	5 (100.0)	1 (100.0)	14 (100.0)
6-weeks				
	Non-compliant	3 (60.0)	1 (100.0)	5 (35.7)
	Compliant	2 (40.0)	0 (0.0)	9 (64.3)
3-months				
	Non-compliant	4 (80.0)	0 (0.0)	4 (30.8)
	Compliant	1 (20.0)	1 (100.0)	9 (62.9)
6-months				
	Non-compliant	4 (80.0)	0 (0.0)	2 (15.4)
	Compliant	1 (20.0)	1 (100.0)	11 (84.6)
1-year				
	Non-compliant	4 (80.0)	0 (0.0)	3 (21.4)
	Compliant	1 (20.0)	1 (100.0)	11 (78.6)

Overall, compliance was higher for White men compared to Black men at each timepoint of follow-up. At 6-weeks follow-up, 64.3% of the White males were compliant compared to 40% of Black males. Compliance increased to 84.6% and 78.6% for the White patients at the 6-months and 1-year timepoints, respectively, compared to just 20% compliance at both time points for the Black males. The one male of mixed ethnicity was compliant at each timepoint of follow-up except for at 6-weeks post radiotherapy.

Table 42: Compliance vs noncompliance at each timepoint of follow-up based on the socioeconomic status of the patient population.

Socioeconomic status		High (n(%))	Middle (n(%))	Low (n(%))
Baseline				
	Non-compliant	0 (0.0)	0 (0.0)	0 (0.0)
	Compliant	4 (100.0)	8 (100.0)	8 (100.0)
6-weeks				
	Non-compliant	2 (50.0)	4 (50.0)	3 (37.5)
	Compliant	2 (50.0)	4 (50.0)	5 (62.5)
3-months				
	Non-compliant	1 (25.0)	4 (57.1)	3 (37.5)
	Compliant	3 (75.0)	3 (42.9)	5 (62.5)
6-months				
	Non-compliant	0 (0.0)	4 (57.1)	2 (25.0)
	Compliant	4 (100.0)	3 (42.9)	6 (75.0)
1-year				
	Non-compliant	1 (25.0)	4 (50.0)	2 (25.0)
	Compliant	3 (75.0)	4 (50.0)	6 (75.0)

Compliance was comparable across the three socioeconomic status levels (high, middle, and low) at the 6-week timepoint (50%, 50%, and 62.5% respectively). At the three month and 6-month timepoints, men of a higher socioeconomic status were more compliant than men of middle and low socioeconomic status. Interestingly, the prostate cancer men of middle socioeconomic status were less compliant at the 3-month, 6-month, and 1-year timepoint compared to both the high and low socioeconomic groups. Compliance within this group remained at around 50% across each timepoint of EPIC-26 administration.

Table 43: Compliance vs noncompliance at each timepoint of follow-up based on the age of the patient population.

Age categories		50-54 (n(%))	55-59 (n(%))	60-64 (n(%))	65-69 (n(%))	70-74 (n(%))	75-79 (n(%))	80-84 (n(%))
Baseline								
	Non-compliant	0 (0.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Compliant	1 (100.0)	3 (100.0)	2 (100.0)	4 (100.0)	6 (100.0)	3 (100.0)	1 (100.0)
6-weeks								
	Non-compliant	1 (100.0)	2 (66.7)	0 (0.0)	1 (25.0)	3 (50.0)	2 (66.7)	0 (0.0)
	Compliant	0 (0.0)	1 (33.3)	2 (100.0)	3 (75.0)	3 (50.0)	1 (33.3)	1 (100.0)
3-months								
	Non-compliant	1 (100.0)	1 (33.3)	0 (0.0)	1 (33.3)	3 (50.0)	1 (33.3)	1 (100.0)
	Compliant	0 (0.0)	2 (66.7)	2 (100.0)	2 (66.7)	3 (50.0)	2 (66.7)	0 (0.0)
6-months								
	Non-compliant	1 (100.0)	1 (33.3)	0 (0.0)	1 (33.3)	2 (33.3)	1 (33.3)	0 (0.0)
	Compliant	0 (0.0)	2 (66.7)	2 (100.0)	2 (66.7)	4 (66.7)	2 (66.7)	1 (100.0)
1-year								
	Non-compliant	1 (100.0)	1 (33.3)	0 (0.0)	1 (25.0)	3 (50.0)	1 (33.3)	0 (0.0)
	Compliant	0 (0.0)	2 (66.7)	2 (100.0)	3 (75.0)	3 (50.0)	2 (66.7)	1 (100.0)

Compliance was next described by the age of the prostate cancer patients at completion of the baseline questionnaire. The youngest male recruited to the feasibility study (age category 50-54 years) was noncompliant at each timepoint of follow-up. Contrastingly, the oldest patient (aged between 80-84 years) successfully completed the EPIC-26 PROM at each timepoint of the study. Similarly, the two prostate cancer patients aged between 60-64 years were also compliant with EPIC-26 completion at each timepoint. Only one of the patients in each of the 55-59 years and 75-79 years age categories was compliant at 6-weeks but this increased to 66.7%, or two of the three patients, at the subsequent follow-ups.

With regards to implementation provider adoption, tasks associated with feasibility study recruitment and the collation of questionnaires were primarily undertaken by radiographers specialising in prostate cancer. During the development phase of the feasibility study, five radiographers were actively engaged in the design process and commenced recruitment of the consecutive patients. At the point of quantitative appraisal, however, it was identified that only one radiographer remained actively engaged in this process. Indeed, one radiographer had been redeployed to the ICU department of the Trust, to provide critical support during the COVID-19 pandemic. Another radiographer was seconded to a management position within the hospital, and

no recruitment occurred to fill these open positions within the radiography department during the feasibility study period. As such, the three remaining radiographers were required to adjust their capacities to additionally take on the workloads of the two open positions and the implementation study was deemed lower priority compared to the routine tasks involved in the day-to-day operations of the clinical setting.

6.2.4 Discussion

Overall, this study aimed to quantitatively evaluate the feasibility study described in Chapter V through questionnaire-based and provider assessment of various outcomes of implementation. As part of this study, a questionnaire investigating acceptability, appropriateness, and feasibility was distributed to the patients recruited to the feasibility study, and uptake was independently assessed at the provider level in terms of patient compliance with PROM completion and implementation provider uptake. The results of the evaluative questionnaire were positive, with patients largely deeming the implementation programme as acceptable, appropriate, and feasible. Despite this, some issues with patient and provider compliance were identified at various timepoints across the feasibility study follow-up period, which in turn impacted the effectiveness of the implementation programme.

Interestingly, patients indicated that their preferred method for completing PROMs electronically was through an email link. This preference was observed despite the majority of patients utilising a mobile phone to access the REDCap platform from the email link. It may be that patients experience increased worry or uncertainty around receiving text messages related to their health or treatment compared to emails, which can be drafted to appear more official with the inclusion of NHS and Trust specific logos, headings, and departmental information. Additionally, no patient indicated a preference for utilising a downloadable app to complete PROMs. This finding may be explained by the characteristics of the patients served by the catchment area of the hospital; significant health inequality exists across Southeast London in terms of the ethnic diversity of patients, socioeconomic status, the ageing population, and patient illiteracy related to health and digital solutions. This is also pertinent, as the MyChart patient portal of the centralised EPIC patient health record platform is accessed using a specific iOS or Android application. These findings indicate that once the EPIC platform goes live at Guy's and St Thomas' NHS Foundation Trust in April 2023, provisions will need to be made to enable the continued administration of PROMs using email links. Indeed, internally generated figures estimate that only 20-30% of the entire patient population of Guy's and St Thomas' NHS Foundation Trust will successfully utilise MyChart, potentially as a result of the significant health inequality explained above. These estimated figures in turn provide further robust evidence to favour the continued support of the REDCap infrastructure for the purposes of

monitoring patient quality of life, past the go-live of EPIC at this site. Overall, patients indicated that the REDCap platform was user friendly and easy to access, and no patient reported any issues with completing their PROMs using this method.

The feasibility study was set-up using the REDCap platform owing to financial constraints, as REDCap is free to download, and due to the availability of data management functionality which was not replicable in DrDoctor. As described above, patients also implied a preference for receiving the quality-of-life questionnaires through email link, which provided further data to favour REDCap over DrDoctor. Despite this, some limitations exist with use of the REDCap platform, including the inability to enable clinical interoperability functionality permitting the automated integration of quality-of-life data with the clinical datapoints stored on the electronic health record platforms. As such, further research occurred to appraise the availability of alternate platforms for the purposes of routine clinical PROM collection in this NHS setting. Specifically, Careology and Vinehealth were investigated as potential private solutions which could be employed to overcome the interoperability barrier. However, both platforms were associated with significant financial costs and relied on on-going patient use of a downloadable mobile application, which, as described above, was not feasible or appropriate bearing in mind the characteristics of the patient population of Guy's Cancer Centre. In summary, the REDCap platform was deemed the most acceptable, appropriate, cost effective, and sustainable solution for the purposes of routine clinical PROM collection at this site. Further work may be prioritised in the future to set-up the clinical interoperability functionality of REDCap with EPIC, however, in the short term, manual transfer of PROM questionnaire data will need to be undertaken by administrators involved in the PROMs implementation project.

Furthermore, the results from the patient evaluation questionnaire outlined that, despite no patient experiencing any issues with EPIC-26 completion, up to 70% of the population would not know who to contact if they did experience issues with completing the PROMs. At the point of recruitment into the feasibility study, the radiographers provided counselling to patients in terms of expectations around the routine collection of PROMs. Nevertheless, patient compliance with completion of the EPIC-26 questionnaire at each timepoint of follow-up varied indicating that further education on the value of patient-reported outcome measurement, at each timepoint of administration, may be warranted. Almost 90% of surveyed patients believed that an educational tool, specific to PROMs, would be useful in the form of either an online video (45% opted for) or a leaflet (44%). Such educational material emerged as an implementation strategy to improve the intervention and permit scale-up and sustainability across Guy's Cancer Centre.

On average, patients remarked that the EPIC-26 questionnaire took approximately 15 minutes to complete, and that this length of time was acceptable. Additionally, 60% of surveyed patients indicated that they believed that the PROM was not administered frequently enough across timeframe of follow-up. Despite these results, 50% of surveyed participants reported that there was too little time between EPIC-26 administration and four patients highlighted that the maximum frequency of questionnaire completion that would be acceptable to them was 3-monthly. When developing this feasibility study, the follow-up timepoints of PROM administration were decided solely by the healthcare professionals involved in the design process and were based on the clinical follow-up schedule after radiation therapy. The findings of this evaluative questionnaire suggest that patient involvement in this decision-making process is a requisite, to ensure that significant administration burden is not experienced by the clinical teams implementing PROMs or the patients completing PROMs.

Furthermore, at the time of feasibility study undertaking, personalised stratified follow-up (PSFU) was in the process of being rolled out across the UK. PSFU involves remote monitoring of low-risk patients through surveillance tests, which in turn improves access for patients with complex needs requiring more tailored outpatient care. As an example, surveillance tests for prostate cancer patients will involve remote PSA tests which are undertaken by the primary care provider as well as remote patient completion of quality-of-life questionnaires. After these surveillance tests are completed, it is anticipated that triggers will be put in place to highlight patients requiring further clinical management at their treating site. The PSFU will primarily impact patients with low-risk disease, who are not in receipt of active treatment, and patients who have completed active treatment and who have moved into longer-term follow-up for their cancer diagnosis. Alignment will need to be reached on which PROM tools to collect, at which timepoints of longer-term follow-up, and using which electronic modes of administration for the routine clinical collection of PROMs to remain successful. The working group of key stakeholders involved in implementation design and facilitation will therefore need to be expanded to include ambassadors for PFSU.

Largely, the feasibility study patients agreed that the content of the EPIC-26 questionnaire was acceptable. However, some comments did arise related to the crude and sensitive nature of some of the functioning questions included in the sexual subscale of this PROM. Such comments once again highlight the necessity of generating valid thresholds for clinical importance for each of the selected quality of life questionnaires, so that absolute scores for each item at each timepoint can be employed to guide further clinical intervention. Currently, only minimally important differences (MID) have been developed for the EPIC-26 questionnaire, and these are based on mean scores calculated per subscale over timepoints of follow-up. Missing data therefore is an issue with MID

calculation as the mean scores cannot be calculated if a patient has decided that specific items are too sensitive in nature to answer. Equally, MID scores cannot be employed if patients are not compliant with completing PROMs at each specified timepoint of follow-up. Development of thresholds for clinical importance will therefore enable tailored clinical management regardless of missing data, both within the questionnaire and across timepoints.

A proportion of the patient noncompliance observed in this feasibility study may be explained by operational issues related to the internal postal service which arose during follow-up. Patients completing the questionnaires on paper were provided with a stamped addressed return envelope. Issues were experienced in terms of the internal postal service and the correct directing the returned questionnaires to the radiography department of the stakeholders involved in conducting the feasibility study. Several returned PROMs were lost within the internal postage system of the hospital meaning that those patients recorded missing data at timepoints of follow-up. A dedicated address may need to be set-up per department to ensure that PROM questionnaires are directed correctly.

Additionally, this mode of administration is associated with increased costs compared to electronic administration, as adequate funds are required to facilitate posting. The prevalence of health inequalities identified within the catchment area of the hospital dictates that paper administration may need to be continued, to ensure that all patients have an equal opportunity to complete PROMs. Patient education and counselling, along with the provision of iPads in clinic waiting areas, is, however, a potential solution which could be used to transform PROM collection to solely electronic modes in the longer term.

Finally, appraisal of feasibility study provider adoption identified issues related to the uptake and retention of staffing resource across the duration of follow-up. The feasibility study was developed during the COVID-19 pandemic and various staff involved in the initial planning stages were subsequently redeployed. Additionally, the longer-term impact of the COVID-19 pandemic on cancer services translated into an increased workload for the staffing body initially identified to facilitate the implementation of routine clinical PROM collection. As such, evaluation of implementation outcomes associated with this feasibility study highlighted the potential necessity of involvement of administrative staff to undertake the logistics of routine PROM collection. Such roles would need to involve defined time allocations to facilitate the coordination of routine PROM administration and tailored training exercises would be required to educate these staff on the value of the programme.

Additionally, feasibility study evaluation identified a potential role for a dedicated clinical nurse specialist within each department to act as a point of liaison between the administrative staff

involved in the logistics of PROM administration and the clinical staff providing management of patients. This role would be important once thresholds for clinical importance were defined per PROM, to ensure that any disease or treatment related patient symptom and/or toxicity is managed in the correct manner.

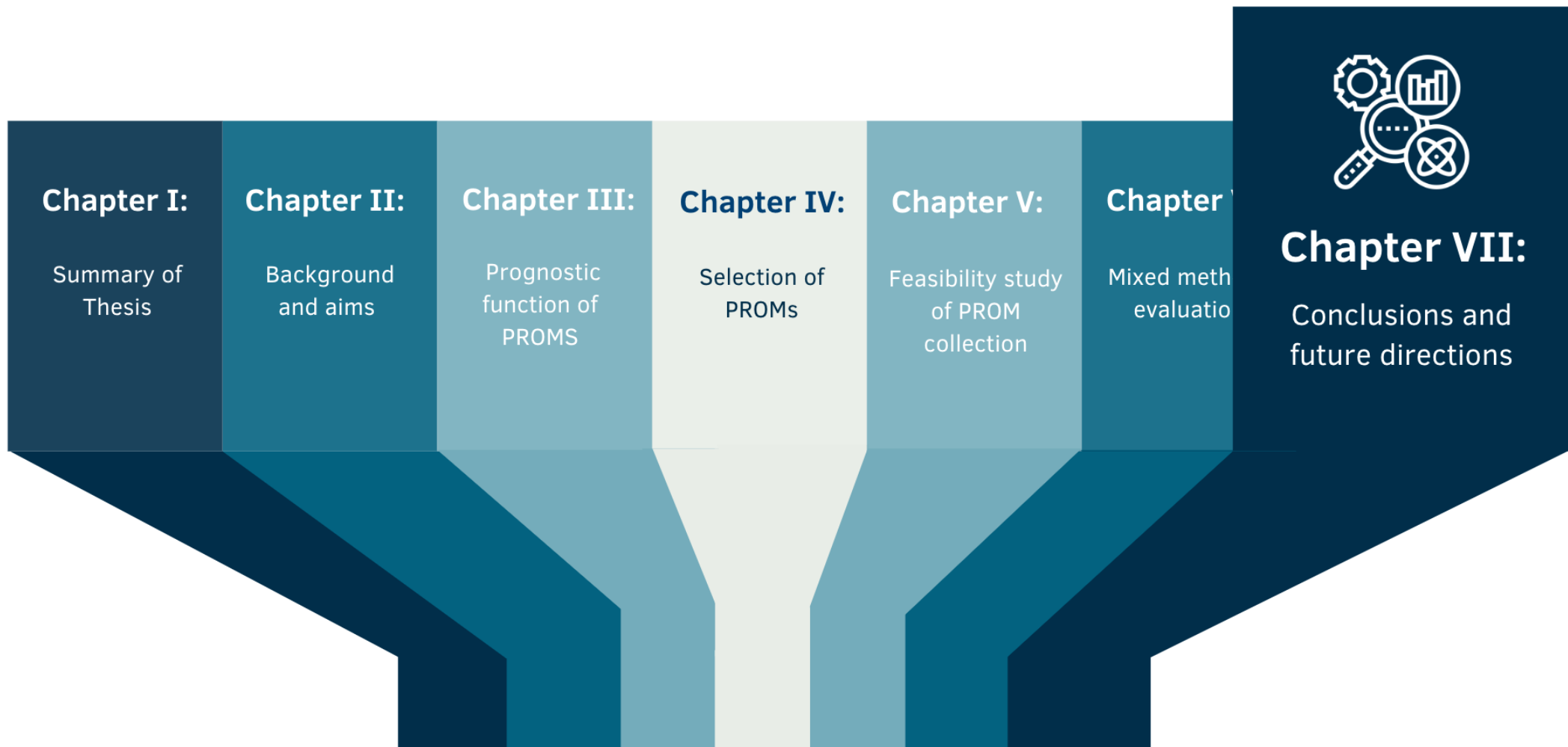
6.2.5 Conclusions

Overall, this study aimed to quantitatively evaluate the feasibility study developed in Chapter V, using defined concepts of Proctor's Implementation Outcomes. Firstly, a questionnaire evaluating notions of acceptability, appropriateness, and feasibility was circulated to patients recruited to the feasibility study before adoption, in terms of patient compliance and provider uptake, was appraised at the provider level. In summary, patients considered the feasibility study of routine clinical PROM collection to be acceptable, appropriate, and feasible. The majority of patients favoured receipt of electronic PROMs through an email link and found the REDCap platform to be user-friendly and intuitive. The study further highlighted the importance of patient involvement in the design of the implementation programme, in terms of defining an acceptable schedule of follow-up. Additionally, the need for tailored education programmes emerged as an important strategy to ensure the sustainability and scale-up of the intervention. Finally, quantitative evaluation of provider uptake identified a need for developing and implementing defined roles to facilitate the administration and interpretation of PROMs in the clinical setting. The embedding of such roles in the clinical setting also aligns with the definition of thresholds for clinical importance for PROMs selected for routine clinical use, to ensure that questionnaire scores are interpreted and actioned appropriately.

Chapter VII:

Conclusions and future directions

Detailed conclusions are provided for each chapter of this thesis before future directions are considered.



7. Chapter VII: Conclusions and future directions

The following chapter provides an overall summary of the conclusions of this thesis, as well as a short discussion on the potential future directions of this work.

7.1 Summary of chapters

On a worldwide scale, owing to continuing advances in healthcare provision, the numbers of cancer patients living with and beyond disease is increasing. As the numbers of patients surviving cancer increases, as does recognition of the need to support patients both in the treatment phase of disease and longer term into survival. Current evidence estimates that more than two thirds of cancer patients have unmet supportive care needs which, in turn, has financial and economic implications for healthcare services, and impacts the outcomes of patients in terms of survival, quality of life and experience. Quality of life therefore forms a critical component of patient care which can be assessed using patient-reported outcome measures (PROMs) however, to date, the routine use of PROMs within NHS clinical settings has been limited, and there exists a lack of defined processes to guide successful implementation within cancer settings specifically.

The overarching aim of the thesis was therefore to identify the critical components necessary for facilitating the successful implementation of routine clinical PROM collection at Guy's Cancer Centre. The thesis employed two, large, sex-specific tumour types for effectiveness, but worked to develop a series of generalised recommendations, or implementation strategies, requiring deliberation when implementing PROMs across routine cancer healthcare settings.

The first study of this thesis (Chapter III) involved a systematic review which was undertaken to assess any prognostic function for collecting PROMs clinically. The justification for this review centred around a paucity of data related to the use of PROMs to improve patient health outcomes in routine clinical cancer settings. Overall, several domains of quality of life were identified as potential prognosticators for oncological outcomes, independently of other clinicopathological features of disease, and the results of this review provide further rationale to support the implementation of routine clinical PROM collection in cancer settings.

Chapter IV of this thesis was formed of three successive projects which were conducted to address an emerging barrier related to the selection of highly valid, reliable, and sensitive PROMs for administration in the routine clinical cancer setting. Project 1 focused on the identification of PRO measures which had been developed for use in, or applied in, populations of patients with tumours of the pelvic abdominal cavity. Projects 2 and 3 then involved psychometric property appraisal of the gynaecological PROMs identified in Project 1, followed by a local consensus process to select PRO

measures for administration in the routine gynaecological and prostate oncology settings of Guy's Cancer Centre. Overall, these successive projects outlined a robust protocol which can be replicated and applied in alternate tumour settings to select highly valid and relevant PROM tools for routine clinical collection. The undertaking of the local consensus process highlighted the importance of engaging stakeholders locally and emphasised the need for alignment at both local and national levels to aid implementation success.

Chapter V of this thesis involved the development of a feasibility study of routine clinical PROM collection in the prostate radiotherapy setting specifically. This feasibility study was developed based on the Medical Research Council guidelines for complex interventions and was implemented for the purposes of process evaluation utilising quantitative and qualitative methodology. Importantly, outcomes assessment of this feasibility study indicated that routine PROM administration is effective for accurately determining disease and treatment related side effects in the cancer clinical setting. Conversely, the feasibility study highlighted the need to perform local assessment of the available supportive care infrastructure to provide effective management for side effects and toxicities associated with disease and treatment. Furthermore, the study emphasised the necessity for defining thresholds for clinical importance to identify patients requiring further clinical management efficiently and effectively within such routine settings.

Chapter VI of this thesis comprised qualitative and quantitative process evaluation of the feasibility study defined in Chapter V. Qualitative evaluation of the feasibility study was guided by the Consolidated Framework for Implementation Research and sought to identify key barriers and facilitators impacting implementation success, scale-up, and sustainability. Once contextual factors impacting the implementation had been identified qualitatively, implementation strategies to overcome such barriers were developed directed by the Expert Recommendations for Implementing Change (CFIR-ERIC) compilation. Emerging implementation strategies included the requirement of tailored training and education for both healthcare professionals and patients, and acquisition of funding. Additionally, recommendations for implementation success centred around technical and clinical team championing, and adaptability of the programme to improve the implementation across clinical settings.

Finally, quantitative evaluation was undertaken in the form of an evaluative questionnaire disseminated to feasibility study participants and through provider-led assessment. Quantitative evaluation was developed based on Proctor's Implementation Outcomes and addressed the acceptability, appropriateness, adoption, and feasibility of routine clinical PROM collection in the prostate radiotherapy setting. Although the implementation was deemed acceptable, appropriate,

and feasible, some issues with patient and provider compliance were identified which impacted the effectiveness of the feasibility study. Quantitative findings identified a role for patient involvement in the design process of PROM implementation in terms of instrument selection and defining timepoints for administration. Additionally, quantitative evaluation demonstrated the existence of health inequalities across cancer patient populations and advocated the set-up of dedicated roles within healthcare systems to support the undertaking of routine PROM administration.

7.2 Overall summary of thesis

This thesis documents the process of defining components which are deemed critical for consideration when implementing routine PROM collection within clinical settings. Critical components impacting implementation success were defined using various methodologies including an internal PROM selection process, as well as qualitative and quantitative evaluation of a novel feasibility study which was developed in the prostate radiotherapy setting of Guy's Cancer Centre.

The following overall conclusions can be drawn from each Chapter of this thesis:

1. The work of this thesis provides further evidence to support the routine use of patient-reported outcome measures (PROMs) within clinical settings. The thesis demonstrates a role for collecting PROMs in routine cancer settings to predict and improve patient health outcomes.
2. The work outlines a replicable protocol which can be employed to select the most appropriate PROM tools for application in routine clinical settings. Tumour specific consensus processes were successfully developed to confer local agreement on the selection of PROM tools. Evidence emerging indicates a role for engaging patients within the selection process for the purposes of defining timepoints for, and frequency of, PROM administration. National and international alignment is also warranted to facilitate benchmarking and comparisons across clinical groups.
3. The work describes the first exploratory attempt to implement routine PROM collection at Guy's Cancer Centre. The results of this intervention infer that routine PROM administration is efficient for conferring the quality-of-life status of prostate cancer patients undergoing radiotherapy treatment. Emerging evidence indicated that the definition of thresholds for clinical importance is critical for ensuring that PROMs can be successfully employed for effective patient management within routine cancer settings.
4. Qualitative evaluation of the feasibility study indicates the requirement of tailored PROM training programmes for healthcare professionals and patients. Additionally, qualitative data reported here has implied the need for clinical and technical championing, as well as

undertaking local needs assessment to ensure the intervention is adaptable based on the requirements of each tumour setting.

5. Quantitative evaluation of the feasibility study advocates the development of novel teams to support the undertaking of routine clinical PROM collection and ensure compliance. Funding was also identified as a critical component for consideration, to provide the required infrastructure to support routine PROM administration within cancer clinical settings.

Overall, this thesis sought to identify and address key issues impacting the routine collection of patient-reported outcome measures across clinical settings. To date, the role of PROMs is well established in research settings, where quality of life questionnaires are used to evaluate the impact of treatment, and provide insight into the effectiveness, appropriateness, and acceptability of novel medical and surgical technologies. Equally, PROMs are widely utilised for healthcare evaluation purposes to examine the impact, quality, and performance of different healthcare services. As an example, at the overarching NHS level, quality of life data collection and reporting is mandated as part of the NHS Cancer Quality of Life Survey as well as tumour specific evaluations such as the National Prostate Cancer Audit (NPCA) (446, 447). Such aggregated national data can be employed to assess individual services and identify areas of improvement, and various examples outlining the value of PROM collection at this level exist at Guy's Cancer Centre. For example, aggregated treatment side effect data collated as part of the NPCA was utilised to alter processes within the prostate radiotherapy setting of this site. Evaluation of the service at Guy's Cancer Centre identified that bowel functioning outcomes were significantly worse compared to other NHS sites, and the service was altered and rebuilt to improve functioning and mitigate such toxicity.

At the individual patient level, repeated administration of PROMs can be used in routine clinical practice to facilitate patient-centred care and assist in shared decision-making. However, PROMs are infrequently collected in routine clinical practice in a standardised format to permit use at the individual patient level. This thesis sought to identify and overcome factors impacting routine clinical PROM collection for the purposes of patient-centred care. The key findings are presented below:

Optimal collection: this thesis highlights the necessity of selecting PROMs which are highly valid, reliable, and sensitive according to assessment of measurement properties. The thesis employed the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) guidelines to appraise each measurement property in a manner which can be easily replicated, and this process further emphasised the requisite of varied published literature, across patient groups and cultures, to support such evaluation. Additionally, the findings of this thesis support the selection of PROM tools which measure domains of interest, and which are well established across research and clinical settings to facilitate benchmarking and auditing.

Moreover, this thesis outlined a need for defining an appropriate administration schedule which aligns with clinical scheduling and follow-up, whilst remaining mindful of patient and clinical team burden. Overall, this thesis demonstrated the successful use of a consensus process within clinical systems, and with local and (inter)national involvement, to successfully select PROMs and define collection schedules. In order to further facilitate patient-centred care, the findings of this thesis suggest a role for the involvement of patients within the selection and scheduling process.

Interpretation and analysis of PROMs: although minimally important differences are defined for some PROMs (including the EPIC-26 tool utilised in the feasibility study of Chapter V), currently no thresholds for clinical importance are defined for most PRO instruments. Minimally important differences are calculated by assessing changes in domain score over time and rely on patient compliance with completion at each timepoint of administration. This thesis identified patient compliance as a barrier to successful routine clinical PROM collection, and therefore suggested a role for thresholds for clinical importance to evaluate patient symptoms and toxicity at each individual timepoint of administration. However, the definition of thresholds for clinical importance is time consuming and requires large international studies involving diverse datasets. As such, this thesis sought to provide suggestions on how PROMs can be utilised meaningfully in the interim period whilst studies defining thresholds are undertaken. In this context, PROMs can be as a method of guiding discussion in clinical consultations, and for highlighting what aspects or issues are of particular importance to the patient as part of value-based healthcare. In the first instance, PROMs can be employed to provide a high-level overview of individual patient symptomology and at the aggregated level to improve or alter services.

How services can be enhanced for patients with “outlier” PROMs: as presented in Chapter V, a large proportion of cancer patients face poor health or disability following cancer treatment. The National Cancer Survivorship Initiative was therefore established as a partnership between NHS England and Macmillan Cancer Support to understand the unmet needs of those living with cancer and develop models of care to meet those needs (448). Overall, collective action is required from healthcare professionals, commissioners, and policymakers to ensure that up-to-date treatment and evidence-based services are available to prevent unnecessary disability. The Survivorship Initiative advocates the provision of long-term effects for GPs to facilitate proactive cancer care reviews, as well as the development of services within the hospital setting to address long term side effects such as erectile dysfunction clinics and andrology clinics. The findings from this thesis provide further evidence to support the significant side effect burden experienced by cancer patients and highlight the need for patient education on potential side effects prior to treatment. Overall, healthcare professionals should ensure patients at risk of or experiencing long-term effects are identified earlier and given

the right information and support. PROMs can be used as a tool to identify these long-term effects and as a means to prioritise those which are most important to the individual patient.

7.3 Future directions

As noted above, the work of this thesis describes the process of identifying components requiring consideration when implementing routine PROM collection in cancer clinical settings. Various components were identified which require addressing prior to this intervention being expanded or further developed. The first step for addressing identified components could involve a further study concerning the development of tailored training and education materials for healthcare professionals and patients. Patient information could be developed in collaboration with patient and public engagement groups within Guy's Cancer Centre, and future study could examine patient compliance with PROM completion following regular dissemination of such educational material. Various modes of delivering patient education could be assessed including leaflets, online videos and in person counselling from healthcare providers, and compliance appraised according to patient characteristics. The issue of engaging patients through education may be circumvented by utilising multiple modes of education which are tailored based on patient demographics and tumour type. Furthermore, future studies could examine the feasibility and acceptability of involving administrative staff in the logistics and operations of administering PROMs routinely in cancer clinical settings. A next iteration of the feasibility study described in Chapter V could be developed to employ administrative staff for the purposes of monitoring PROM administration and completion. Acceptability related to administrative staff involvement could be assessed using qualitative focus groups and interviews with healthcare professionals and patients. Tailored training programs may also need be developed to educate healthcare professionals on the use and value of PROM collection in clinical settings. Different levels of training may be required depending on role, and qualitative methods could be employed to garner insight into the needs of each position and designation.

In addition, future work may wish to address the scoring of PROMs and internally define thresholds for clinical importance. Work to define thresholds for clinical importance is currently limited primarily to cancer generic PROMs and mandates multi-site, international involvement in the form of large cohort studies. Whilst such a study is not feasible at this site, this thesis identified a role for local internal consensus processes to confer agreement on PROM selection and administration. Local consensus processes could therefore be developed, with stakeholder involvement, to define thresholds necessitating further clinical intervention based on internal data from Guy's Cancer Centre specifically.

Finally, future work should include the development of a business case to further support and facilitate the routine collection of PROMs in NHS clinical settings. As demonstrated in this thesis, sufficient staffing resource is required in terms of clinical support to manage routine PROM collection. Additionally, expertise is required in terms of the analysis and interpretation of PROM tools to enable efficient use at the individual patient-level. Future work should therefore involve drafting of a business case which will outline the financial value and potential financial return of routinely implementing PROMs within cancer clinical settings. It is hypothesised that early intervention for symptoms identified using PROMs will ultimately save healthcare trusts money, as well managed cancer patients may not access healthcare services as frequently. Data is required to further investigate this hypothesis, however, and identify whether routine PROM administration does indeed save resources.

To test the implementation strategies identified within this thesis, future study could involve the development of a second round of feasibility testing including all prostate radiotherapy patients or all gynaecological cancer patients. Conversely, the findings of this thesis could be shared with the personalised stratified follow-up pathway programme of Guy's Cancer Centre to inform the roll-out of remote monitoring for patients with low-risk disease. Identified implementation strategies related to patient education, and the definition of thresholds which trigger further clinical management could be tested as part of this wider mandated programme.

Overall, this thesis presents clear evidence to support the implementation of routine PROM collection in cancer clinical settings. Benefits of routine clinical PROM administration were observed for both patients and healthcare professionals, and stakeholders at Guy's Cancer Centre demonstrated willingness to engage in implementation efforts. Despite this rationale, this thesis highlighted multiple complexities associated with commencing routine clinical PROM collection at scale and advocates the continued use of small-scale feasibility testing prior to scale-up, to ensure sustainability. The findings of this thesis include the identification of various barriers which affected the success of routine clinical PROM collection at this site. As outlined in the MRC Framework for Complex Interventions, cyclical processes are required to identify relevant implementation strategies, test such strategies in practice, and amend the process until normalisation, or embedding of routine PROM collection in clinical settings, is established (404). Implementation strategies to address identified barriers have, however, already been identified, and future studies will be developed to assess each strategies' impact on implementation success. Concurrently with the work of this thesis, various alternate NHS cancer sites are working to achieve similar goals in terms of routine PROM implementation. For example, Healthcare Improvement Scotland have recently commenced a national initiative to collect PROMs for prostate cancer patients in the pre- and post-

radical prostatectomy setting (449). As part of this initiative, however, data is being utilised at the aggregated population level, rather than for informing patient-level care. Conversely, the Christie NHS Foundation Trust and NHS Wales are working to implement routine PROM collection in cancer settings for the purposes of patient-centred care (450, 451). Overall, it is therefore justifiable and practical to coordinate PROM implementation efforts across NHS sites and share failings and learnings. Currently, each site is working independently towards the common goal of routine PROM implementation, but it is preferable to work collectively to overcome barriers which are common denominators across NHS sites. Overall, there is an urgent need to facilitate routine clinical PROM collection across the NHS, and, based on the work and results of this thesis, momentum exists to advocate such initiative.

G. References

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REVIEW

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An assessment of the use of patient reported outcome measurements (PROMs) in cancers of the pelvic abdominal cavity: identifying oncologic benefit and an evidence-practice gap in routine clinical practice

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Abstract

Background: Patient reported outcome measurements (PROMs) are emerging as an important component of patient management in the cancer setting, providing broad perspectives on patients' quality of life and experience. The use of PROMs is, however, generally limited to the context of randomised control trials, as healthcare services are challenged to sustain high quality of care whilst facing increasing demand and financial shortfalls. We performed a systematic review of the literature to identify any oncological benefit of using PROMs and investigate the wider impact on patient experience, in cancers of the pelvic abdominal cavity specifically.

Methods: A systematic review of the literature was conducted using MEDLINE (Pubmed) and Ovid Gateway (Embase and Ovid) until April 2020. Studies investigating the oncological outcomes of PROMs were deemed suitable for inclusion.

Results: A total of 21 studies were included from 2167 screened articles. Various domains of quality of life (QoL) were identified as potential prognosticators for oncologic outcomes in cancers of the pelvic abdominal cavity, independent of other clinicopathological features of disease: 3 studies identified global QoL as a prognostic factor, 6 studies identified physical and role functioning, and 2 studies highlighted fatigue. In addition to improved outcomes, a number of included studies also reported that the use of PROMs enhanced both patient-clinician communication and patient satisfaction with care in the clinical setting.

Conclusions: This review highlights the necessity of routine collection of PROMs within the pelvic abdominal cancer setting to improve patient quality of life and outcomes.

Keywords: Patient reported outcome measurements, Health related quality of life, Prognostic factors, Overall survival, Pelvic abdominal cancers

Introduction

The incidence of cancers of the pelvic abdominal cavity (broadly urological, gynaecological, colorectal, gastric, hepatic and pancreatic tumour types) is increasing as population life-expectancy increases [1]. As of 2018,

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Appendix II: Assessment of study quality according to Joanna Briggs Institute checklists, as included in the systematic review assessing the prognostic function of PROMs.

Table 1: JBI quality assessment of included randomised control trials

		S Gourgou- Bourgade et al (2013)	J Bernhar d et al (2010)	C.C.H Stuck y et al (2011)	J Bingene r et al (2015)	D.F. Roychowdhu ry et al (2003)	L Collett e et al (2004)	I Chau et al (2004)
1	Was true randomisation used for assignment of participants to treatment groups?	✓	✓	✓	✓	✓	✓	✓
2	Was allocation to treatment groups concealed?	x	x	x	x	x	U	U
3	Were treatment groups similar at baseline?	✓	✓	✓	✓	✓	✓	✓
4	Were participants blind to treatment assignment?	x	x	x	x	x	U	U
5	Were those delivering treatment blind to treatment assignment?	x	x	x	x	x	U	U
6	Were outcome assessors blind to treatment assignment?	U	U	x	U	x	U	x
7	Were treatment groups treated identically other than the intervention of interest?	✓	✓	✓	✓	✓	✓	✓
8	Was follow-up complete and, if not, were differences between groups in terms of follow-up adequately described and analysed?	✓	✓	✓	✓	✓	✓	✓

9	Were participants analysed in the groups to which they were randomised?	✓	x	✓	x	x	x	x
10	Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	✓	✓
11	Were outcomes measured in a reliable way?	✓	✓	✓	✓	✓	✓	✓
12	Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?	✓	✓	✓	✓	✓	✓	✓

Table 2: JBI quality assessment of included cohort studies

		J Graha m et al (2018)	BH de Rooij et al (2018)	KM Robins on et al (2011)	D Gupt a et al (2015)	R Jayadevapp a et al (2009)	A Coate s et al (1997)	D Braun et al (2012)	BM Baekelan et al (2016)	C Quinte n et al (2013)	N Maise y et al (2002)	S Monin gi et al (2015)
1	Were the two groups similar and recruited from the same population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	Was the exposure measured in a reliable and valid way?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4	Were confounding factors identified?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5	Were strategies to deal with confounding factors stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7	Were the outcomes measured in a valid and reliable way?	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓
8	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	✓	U	x	U	✓	✓	U	✓	✓	✓	U

9	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	U	U	U	U	✓	✓	U	U	✓	✓	U
10	Were strategies to address incomplete follow up utilised?	U	U	U	U	✓	✓	U	U	✓	U	U
11	Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3: JBI quality assessment of included case series

		C Lis et al (2008)	C Lis et al (2006)	U Lehto et al (2018)
1	Were there clear criteria for inclusion in the case series?	✓	✓	✓
2	Was the condition measured in a standard, reliable way for all participants included in the case series?	✓	✓	✓
3	Were valid methods used for identification of the condition for all participants included in the case series?	✓	✓	✓
4	Did the case series have consecutive inclusion of participants?	✓	✓	✓
5	Did the case series have complete inclusion of participants?	✓	✓	x
6	Was there clear reporting of the demographics of the participants in the study?	✓	✓	x
7	Was there clear reporting of clinical information of the participants?	✓	✓	x
8	Were the outcomes or follow-up results of cases clearly reported?	✓	✓	✓
9	Was there clear reporting of the presenting site(s)/clinical(s) demographic information?	✓	✓	U
10	Was statistical analysis appropriate?	✓	✓	✓

Appendix III: Study characteristics and PROM instrument(s) identified in each included gynaecological cancer article.

Study ID	Title	PROMs	RCT	Setting	Trt Modality	Patient Number	Outcome
5138	Health-related quality of life in cervical cancer survivors: a population-based survey.	SF-36, EQ-5D, EORTC QLQ-CX24, State Trait Anxiety Inventory	No	Survivors	All	349	Primary
1040	Adaptation and quality of life among long-term cervical cancer survivors in the military health care system.	SF-36	No	Survivors	All	41	Primary
4953	Quality of life and sexual, bladder, and intestinal dysfunctions after class III nerve-sparing and class II radical hysterectomies: a questionnaire-based study.	FACT-Cx	No	All	Surgery	157	Primary
1019	A pilot study of Auron Misheil Therapy in patients with advanced cervical cancer: tumor response and its correlation with clinical benefit response, and preliminary quality of life data.	EORTC QLQ-C30	No	Advanced	Auron Misheil Therapy	15	Secondary
4884	Psychological distress and quality of life in cervical cancer survivors after radiotherapy: do treatment modalities, disease stage, and self-esteem influence outcomes?.	Hospital Anxiety and Depression Scale, FACT-G, Ronsenberg Self-esteem Scale	No	Survivors	Chemoradiotherapy, radiotherapy	60	Primary

4812	Patients' acceptance and psychometric properties of the EORTC QLQ-CX24 after surgery.	EORTC QLQ-CX24, EORTC QLQ-C30, Hospital Anxiety and Depression Scale	No	All	Surgery	134	Secondary
4796	Validation of EQ-5D in patients with cervical cancer in Taiwan.	EQ-5D, EORTC QLQ-C30	No	All	All	530	Primary
4710	Surviving cervical cancer: does health-related quality of life influence survival?.	FACT-CX, SF-12	No	Survivors	All	353	Primary
4680	A comparison of quality-of-life domains and clinical factors in ovarian cancer patients: a Gynecologic Oncology Group study.	FACT-O	No	Advanced	Surgery, Chemotherapy		Primary
4597	A 2-year prospective study assessing the emotional, sexual, and quality of life concerns of women undergoing radical trachelectomy versus radical hysterectomy for treatment of early-stage cervical cancer.	Female Sexual Functioning Inventory, CES-D Scale, IES-Scale	No	Early Stage	Surgery	71	Primary
4590	Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: a Gynecologic Oncology Group study.	FACT-Cx, FACT-GOG, Neurotoxicity Scale, Brief Pain Inventory	Yes	Advanced	Chemotherapy	513	Primary
4197	The quality of life of women treated for cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Early Stage	Surgery	100	Primary

4265	Quality of life among Thai women diagnosed with cervical cancer and cervical intraepithelial neoplasia at King Chulalongkorn Memorial Hospital.	FACT-G	No	All	All	172	Primary
4146	Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: a prospective, longitudinal study.	EORTC QLQ-C30, EORTC QLQ-CX24, Hospital Anxiety and Depression Scale	No	Early Stage	Surgery, Chemoradiation		Primary
4124	The association between quality of life domains and overall survival in ovarian cancer patients during adjuvant chemotherapy: a Gynecologic Oncology Group Study.	FACT-G	Yes	Stage III	Chemotherapy	415	Primary
4067	Quality of life and survival in advanced cervical cancer: a Gynecologic Oncology Group study.	FACT-Cx	No	Advanced	All	991	Primary
3966	Quality of life characteristics inpatients with cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	All	All	346	Primary
3760	Health-related quality of life and associated factors in Chinese women with cervical cancer: a 9-month follow-up.	FACT-CX	No	All	All	187	Primary
3746	Quality of life in cervical cancer patients treated with radiation therapy.	EORTC QLQ-C30	No	All	Radiotherapy	205	Primary

3650	Long-term prospective longitudinal evaluation of emotional distress and quality of life in cervical cancer patients who remained disease-free 2-years from diagnosis.	EORTC QLQ-C30, EORTC QLQ-CX24, Hospital Anxiety and Depression Scale	No	Early, Locally Advanced	All	227	Primary
1117	Evaluation of the psychometric properties of the Functional Assessment of Cancer Therapy-Cervix questionnaire in Brazil.	FACT-CX, SF-36	No	All	All	100	Primary
3171	Quality of life and mental health in Brazilian women treated for invasive carcinoma of the cervix.	SF-36, State Trait Anxiety Inventory, 12-item General Health Questionnaire	No	Survivors	All	114	Primary
3153	Quality of life in women with cervical precursor lesions and cancer: a prospective, 6-month, hospital-based study in China.	EQ-5D	No	All	All	194	Primary
807	Health-related quality of life in older adult survivors of selected cancers: data from the SEER-MHOS linkage.	SF-36, RAND 12-Item Health Survey	No	All	All	17,000 overall	Primary
2805	Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Advanced	Radiotherapy, Chemotherapy, Brachytherapy	50	Primary

2742	Quality of life, urogynecological morbidity, and lymphedema after radical vaginal trachelectomy for early-stage cervical cancer.	EORTC QLQ-CX24	No	Early Stage	Surgery	50	Secondary
2388	Sexual function, depression, and quality of life in patients with cervical cancer.	Female Sexual Function Index, Hospital Anxiety and Depression Scale, FACT-G	No	All	All	137	Primary
2385	Sexual function and quality of life in women with cervical cancer before radiotherapy: a pilot study.	Female Sexual Function Index, WHO questionnaire	No	All	Radiotherapy	80	Primary
2382	Sexual function of women surviving cervical cancer.	Female Sexual Function Index	No	Survivors	All	37	Primary
2503	Prospective quality of life study of South African women undergoing treatment for advanced-stage cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Advanced	Chemoradiation	219	Primary
2227	Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Locally Advanced	Chemotherapy, Radiotherapy, Brachytherapy	744	Primary
2213	Health-Related Quality of Life and Sociodemographic Characteristics as Prognostic Indicators of Long-term Survival in Disease-Free Cervical Cancer Survivors.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Survivors	All	860	Primary

2203	Health Behaviors in Cervical Cancer Survivors and Associations with Quality of Life.	FACT-Cx, Brief Symptom Inventory, Patient-Reported Outcomes Measurement Information System	No	Survivors	All	204	Primary
1024	Survey of cervical cancer survivors regarding quality of life and sexual function.	FACT-Cx, FACIT-Spiritual, Female Sexual Functioning Index	No	Survivors	All	140	Primary
2034	Long-term Pelvic Floor Function and Quality of Life After Radical Surgery for Cervical Cancer: A Multicenter Comparison Between Different Techniques for Radical Hysterectomy With Pelvic Lymphadenectomy.	EORTC QLQ-C30, EORTC QLQ-CX24, Leiden Questionnaire	No	Early Stage	Surgery	268	Primary
1966	Quality of life after radical trachelectomy for early-stage cervical cancer: A 5-year prospective evaluation.	General Health-Related QoL, FACT-Cx, MD Anderson Symptom Inventory, Female Sexual Functioning Index, Satisfaction with Decision Scale	No	Early Stage	Surgery	39	Primary
1827	Long-Term Morbidity and Quality of Life in Cervical Cancer Survivors: A Multicenter Comparison Between Surgery and Radiotherapy as Primary Treatment.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Early Stage	Surgery, Radiotherapy	323	Primary
1700	Quality of life of breast and cervical cancer survivors.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Survivors	All	75	Primary

1629	Quality of life among survivors of early-stage cervical cancer in Taiwan: an exploration of treatment modality differences.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Early Stage	Surgery, Chemoradiation	290	Primary
1545	Dynamics of patient reported quality of life and symptoms in the acute phase of online adaptive external beam radiation therapy for locally advanced cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Locally Advanced	Radiotherapy	138	Primary
791	A Comparison of EQ-5D-3L Index Scores Using Malaysian, Singaporean, Thai, and UK Value Sets in Indonesian Cervical Cancer Patients.	EQ-5D	No	All	All	87	Secondary
489	Assessment of Quality of Life and Urinary and Sexual Function After Radical Hysterectomy in Long-Term Cervical Cancer Survivors.	EORTC QLQ-CX24, EORTC QLQ-C30, Incontinence Impact Questionnaire	No	Survivors	Surgery	251	Primary
188	The Health related Quality of Life of Puerto Ricans during Cancer Treatments; A Pilot Study.	FACT-G	No	All	All	8	Primary
1334	Physician assessed and patient reported lower limb edema after definitive radio(chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: A report from the EMBRACE study.	EORTC QLQ-CX24	No	All	Radiochemotherapy, brachytherapy	1176	Secondary

650	Supportive care needs and quality of life of patients with gynecological cancer undergoing therapy.	EORTC QLQ-C30, EORTC QLQ-CX24	No	All	All	153	Secondary
717	Quality of life of cervical cancer patients after completion of treatment - A study among Bangladeshi women.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Survivors	All	109	Primary
360	A comparative analysis of quality of life after postoperative intensity-modulated radiotherapy or three-dimensional conformal radiotherapy for cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	All	Radiotherapy	64	Secondary
112	Health-related Quality of Life in Women with Cervical Cancer.	FACT-CX	No	All	All	115	Secondary
95	An exploration into the quality of life of women treated for cervical cancer.	EORTC QLQ-C30, EORTC QLQ-CX24	No	All	Radiotherapy, Brachytherapy	153	Primary
174	Health-related quality of life in locally advanced cervical cancer patients treated with neoadjuvant therapy followed by radical surgery: A single-institutional retrospective study from a prospective database.	EORTC QLQ-C30, EORTC QLQ-CX24	No	Locally Advanced	All	275	Primary
4979	Impact of cancer on health-related quality of life of older Americans.	Medical Outcomes Study	No	All	All		Primary

4968	Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial.	EORTC QLQ-C30, EORTC-QLQ-PR25, EORTC QLQ-OV28	Yes		Radiotherapy or Brachytherapy	427	Secondary
4892	Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study.	FACT-G	Yes	All	Surgical	802	Primary
4626	Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial.	FACT-G	Yes	Stage 1	Surgical	361	Primary
4490	Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24).	EORTC QLQ-EN24	No	All	All	268	Primary
4383	Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial.	SF-36, EORTC QLQ-PR25, EORTC QLQ-OV28, EORTC QLQ-CX24	Yes	Stage 1	Radiotherapy	351	Primary

3959	Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study.	SF-36, EORTC QLQ-EN24	No	Survivors	Radiotherapy	742	Primary
3175	Evaluation of quality of life and emotional distress in endometrial cancer patients: a 2-year prospective, longitudinal study.	EORTC QLQ-C30, EORTC QLQ-CX24, Hospital Anxiety and Depression Scale (HADS)	No	All	All		Primary
2470	Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial.	EORTC QLQ-C30, subscales for bowel and bladder symptoms, Impact of Cancer Questionnaire	Yes	Stage I Survivors	Radiotherapy	427	Primary
2049	Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial.	EORTC QLQ-C30	Yes	High risk	Chemoradiotherapy	686	Secondary
1457	Independent psychometric validation of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24).	EORTC QLQ-EN24, EORTC QLQ-C30	No	All	All	284	Primary

1785	Sexual Function and Quality of Life Among Patients With Endometrial Cancer After Surgery.	FACT-G, Female Sexual Function Index	No	Survivors	All	118	Primary
1760	Physical activity-related differences in body mass index and patient-reported quality of life in socioculturally diverse endometrial cancer survivors.	FACT-En	No	Survivors	All	62	Secondary
1321	Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer.	FACT-G, EQ-5D, Brief Pain Inventory (BPI)	No	All	Surgical	468	Primary
230	Optimistic, realistic, and pessimistic illness perceptions; quality of life; and survival among 2457 cancer survivors: the population-based PROFILES registry.	EORTC QLQ-C30	No	Survivors	All		Secondary
421	Long-term quality of life after comprehensive surgical staging of high-risk endometrial cancer - results from the RASHEC trial.	EORTC QLQ-C30, EORTC EN-24, EQ-5D	No	High risk	Surgical	120	Primary
118	Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis.	EORTC QLQ-C30	No	Survivors	All	221	Primary

4108	Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data.	EORTC QLQ-C30, EORTC QLQ-PR25, EORTC QLQ-OV28	Yes	High-intermediate risk	Radiotherapy	427	Primary
4090	The quality of sexual life in women with gynaecological cancers.	Sexual Quality of Life Questionnaire, Multidimensional Scale of Perceived Social Support	No	All	All	80	Primary
3969	Prospective assessment of quality of life and psychological distress in patients with gynecologic malignancy: a 1-year prospective study.	EORTC QLQ-C30, EORTC QLQ-CX24, Hospital Anxiety and Depression Scale	No	All	Radiotherapy	57	Primary
1106	Sexual functioning and vaginal changes after radical vaginal trachelectomy in early stage cervical cancer patients: a longitudinal study.	Female Sexual Function Index	No	Early Stage	Surgery	18	Primary
2858	Fatigue and quality of life in women treated for various types of gynaecological cancers: a cross-sectional study.	SF-36, Hospital Anxiety and Depression, Fatigue Questionnaire	No	Survivors	All	120	Primary

1148	Feeling powerless: Locus of control as a potential target for supportive care interventions to increase quality of life and decrease anxiety in ovarian cancer patients.	Locus of control scale, FACT-O,FACIT-Sp, Edmonton Symptom Assessment Score, Hospital Anxiety and Depression, Templers Death Anxiety Scale, Herth Hope Index	No	Locally advanced/Advanced	All	104	Secondary
1532	Pelvic radiotherapy does not deteriorate the quality of life of women with gynecologic cancers in long-term follow-up: A 2 years prospective single-center study.	EORTC QLQ-C30, EORTC QLQ-CX24, Hospital Anxiety and Depression Scale	No	All	Radiotherapy	100	Primary
1289	Patient reported outcomes in evaluation of chemotherapy toxicity in women with gynecologic malignancies: A pilot study.	PRO version of CTCAE	No	All	Chemotherapy	44	Secondary
581	Effects of leuprorelin for the treatment of recurrent gynecological cancer by assessment including self-administered quality-of-life questionnaire.	The questionnaire of physical well-being	No	Recurrent	Hormone Therapy	25	Primary
595	A correlation study of fear of cancer recurrence, illness representation, self-regulation, and quality of life among gynecologic cancer survivors in Taiwan.	Assessment of Survivor Concerns, Brief Illness Perception Questionnaire, Self-Regulation Questionnaire, EORTC QLQ-C30	No	Survivors	All	287	Primary

102	Sexual quality of life after the treatment of gynecologic cancer: what women want.	Changes in Sexual Function Questionnaire	No	Survivors	All	85	Primary
5409	Measuring health-related quality of life and neutropenia-specific concerns among older adults undergoing chemotherapy: validation of the Functional Assessment of Cancer Therapy-Neutropenia (FACT-N).	FACT-N	Yes	All	Chemotherapy		Primary
5392	The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer.	EORTC QLQ-C30	Yes	Advanced	Chemotherapy	151	Primary
4491	Prospective assessment of quality of life in long-term ovarian cancer survivors.	EORTC QLQ-C30	No	Survivors	All	33	Primary
4250	Health-related quality of life outcomes of docetaxel/carboplatin combination therapy vs. sequential therapy with docetaxel then carboplatin in patients with relapsed, platinum-sensitive ovarian cancer: results from a randomized clinical trial.	FACT-O	Yes	Recurrent	Chemotherapy	296	Secondary

4121	Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: a nationwide Danish study.	EORTC QLQ-C30	No	All	All	723	Secondary
4111	Spiritual well-being and quality of life of women with ovarian cancer and their spouses.	FACIT-Spiritual Well-Being, Symptom Distress Scale, FACIT-Ovarian	No	All	All	70	Primary
4072	Health-related quality of life in recurrent platinum-sensitive ovarian cancer--results from the CALYPSO trial.	EORTC QLQ-C30, EORTC QLQ-OV28	Yes	Recurrent	Chemotherapy		Primary
3942	Patient-reported outcomes in relapsed ovarian cancer: results from a randomized Phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD alone.	EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D	Yes	Recurrent	Chemotherapy	672	Primary
3776	Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is it worth the risk?.	EORTC QLQ-C30	No	All	Surgery, Chemotherapy	90	Primary
3876	Health-related quality of life during sequential chemotherapy with carboplatin followed by weekly paclitaxel in advanced ovarian cancer: a multicenter phase ii study of the North Eastern German Society of Gynecological Oncology.	EORTC QLQ-C30, EORTC QLQ-OV28	Yes	All	Chemotherapy	104	Primary

3728	Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study.	FACT-O	Yes	Advanced	Chemotherapy	1693	Secondary
3703	Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial.	EORTC QLQ-C30	Yes	High risk	Chemotherapy	1528	Primary
3336	Quality of life and treatment response among women with platinum-resistant versus platinum-sensitive ovarian cancer treated for progression: a prospective analysis.	FACT-O	No	Recurrent	Chemotherapy	172	Primary
3283	Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II-IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016).	FACT-G, FACT-O, FACT-T	Yes	Advanced	Chemotherapy	637	Primary
1004	Quality of life in ovarian cancer patients choosing to receive salvage chemotherapy or palliative treatment.	FACT-G	No	Recurrent	Chemotherapy	38	Secondary

1166	The impact of epithelial ovarian cancer diagnosis on women's life: a qualitative study.	Psychological General Well-being Index	No	All	All	39	Secondary
3154	Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer.	EORTC QLQ-OV28, FACT-O	Yes	Advanced	Chemotherapy	361	Primary
3090	Development of the measure of ovarian symptoms and treatment concerns: aiming for optimal measurement of patient-reported symptom benefit with chemotherapy for symptomatic ovarian cancer.	EORTC QLQ-C30, EORTC QLQ-OV28, FACT-O, Measure of Ovarian Symptoms and Treatment	No	Advanced	Chemotherapy		
999	Coping and quality of life in Turkish women living with ovarian cancer.	COPE	No	All	Chemotherapy	228	Primary
2961	Determinants of quality of life in ovarian cancer survivors: a pilot study.	EORTC QLQ-C30, EORTC QLQ-OV28	No	Survivors	All	102	Primary
1160	Dietary habits changes and quality of life in patients undergoing chemotherapy for epithelial ovarian cancer.	EORTC QLQ-C30, EORTC QLQ-OV28	No	All	Chemotherapy	61	Secondary
2943	Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: results from the population-based PROFILES registry.	EORTC QLQ-C30, EORTC QLQ-OV28	No	Survivors	All	348	Primary

1156	Self-reported distress in patients with ovarian cancer: is it related to disease status?.	Distress Thermometer, Hospital Anxiety and Depression Scale, Impact of Event Scale	No	All	All	273	Primary
1151	Quality of life after early enteral feeding versus standard care for proven or suspected advanced epithelial ovarian cancer: Results from a randomised trial.	FACT-G, FACT-O	Yes	Advanced	Surgery	109	Secondary
2610	Disease-free ovarian cancer patients report severe pain and fatigue over time: prospective quality of life assessment in a consecutive series.	MAYO 10-point linear scale	No	All	Chemotherapy	59	Primary
2540	Body mass index, physical activity and quality of life of ovarian cancer survivors: time to get moving?.	EORTC QLQ-C30, EORTC QLQ-OV28	No	Survivors	All	293	Secondary
2502	Patient-Reported Outcomes After Extensive (Ultraradical) Surgery for Ovarian Cancer: Results From a Prospective Longitudinal Feasibility Study.	EORTC QLQ-C30, EORTC QLQ-OV28	No	All	Surgery	93	Primary
2163	Health-related quality of life in women with recurrent ovarian cancer receiving paclitaxel plus trebananib or placebo (TRINOVA-1).	FACT-O, EQ-5D	Yes	Recurrent	Chemotherapy	919	Primary

2158	Using Patient-reported Outcomes to Compare Relative Burden of Cancer: EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer.	EQ-5D, FACT-G	No	Advanced	All	50	Primary
2148	Health-related quality of life in ovarian cancer survivors: Results from the American Cancer Society's Study of Cancer Survivors - I.	SF-36	No	Survivors	All	365	Primary
2018	Sexual Health and Quality of Life Assessment among Ovarian Cancer Patients during Chemotherapy.	EORTC QLQ-OV28, Female Sexual Function Index, Female Sexual Distress Scale	No	All	Chemotherapy	49	Primary
1882	Ovarian cancer study dropouts had worse health-related quality of life and psychosocial symptoms at baseline and over time.	FACT-O, Hospital Anxiety and Depression Scale, Life Orientation Test, Insomnia Severity Index	No	All	All	619	Primary
1943	Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer.	FACT-O, FACT-O FOSI	Yes	Recurrent	Monotherapy	265	Primary
1130	Pre-diagnosis health-related quality of life, surgery, and survival in women with advanced epithelial ovarian cancer: A SEER-MHOS study.	SF-36, Veterans-RAND-12	No	Advanced	All	374	Primary
1085	Quality of life with cediranib in relapsed ovarian cancer: The ICON6 phase 3 randomized clinical trial.	EORTC QLQ-C30	Yes	Recurrent	Chemotherapy	456	Secondary

1453	Symptom Clusters and Quality of Life According to the Survivorship Stage in Ovarian Cancer Survivors.	EORTC QLQ-C30, EORTC QLQ-OV28	nO	Survivors	All	182	Secondary
1126	Quality of life among long-term survivors of advanced stage ovarian cancer: A cross-sectional approach.	FACT-O, CESD, SPS, IPAQ-SF	No	Survivors	All	56	Primary
793	Changes in spiritual well-being and psychological outcomes in ovarian cancer survivors.	FACIT-Spiritual Well-Being, Center for Epidemiological Studies Depression Scale, Impact of Event Scale, Profile of Moods States	No	All	Surgery	241	Primary
1125	Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: An ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study.	FACT-O	Yes	Advanced	Chemotherapy	1152	Primary
1400	Measuring what matters MOST: validation of the Measure of Ovarian Symptoms and Treatment, a patient-reported outcome measure of symptom burden and impact of chemotherapy in recurrent ovarian cancer.	Measure of Ovarian Symptoms, EORTC QLQ-C30, EORTC QLQ-OV28, FACT-O	No	Stage II	Chemotherapy	948	Secondary

17	Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters-patient-centered end points in trials of maintenance therapy.	EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D	Yes	All	Chemotherapy	940	Secondary
592	Health-related quality of life and pelvic floor dysfunction in advanced-stage ovarian cancer survivors: associations with objective activity behaviors and physiological characteristics.	SF-36, Australian Pelvic Floor Questionnaire	No	Survivors	All	20	Primary
15	Quality-of-life analysis of the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG study comparing platinum-based versus non-platinum-based chemotherapy in patients with partially platinum-sensitive recurrent ovarian cancer.	EORTC QLQ-C30, EORTC QLQ-OV28	Yes	Recurrent	Chemotherapy	215	Secondary
943	Course of chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer patients: A longitudinal study.	EORTC QLQ-C30, EORTC QLQ-OV28	No	All	Chemotherapy	174	Secondary

704	Quality of life, symptoms and care needs in patients with persistent or recurrent platinum-resistant ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study.	FACIT-F, FACT-O, Disease Related Symptoms, Treatment Side Effects, Function/Well-being	No	Recurrent	All	102	Primary
789	Disparities in health-related quality of life in women undergoing treatment for advanced ovarian cancer: the role of individual-level and contextual social determinants.	FACT-O	Yes	Advanced	Chemotherapy	993	Primary
1023	Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial.	FACT-O, EQ-5D	Yes	Recurrent	Chemotherapy	553	Secondary
1027	Randomized Trial of Exercise on Quality of Life in Women With Ovarian Cancer: Women's Activity and Lifestyle Study in Connecticut (WALC).	SF-36, FACT-F	Yes	Survivors	All	144	Secondary
352	Older ovarian cancer survivors report lower long-term health-related quality of life than younger survivors: A study from the population-based profiles registry.	EORTC QLQ-C30	No	Survivors	All	348	Primary

291	Determinants of health-related quality of life in elderly ovarian cancer patients: The role of frailty and dependence.	EORTC QLQ-C30	No	All	All	84	Primary
160	OVQUEST - Life after the diagnosis and treatment of ovarian cancer - An international survey of symptoms and concerns in ovarian cancer survivors.	OvQuest	No	All	Chemotherapy	1360	Primary
3056	Quality of life, body mass index, and physical activity among uterine cancer patients.	FACT-GOG	No	Survivors	All	213	Secondary
1363	Health-Related Quality of Life of Patients with HPV-Related Cancers in Indonesia.	EQ-5D	No	All	All		Primary
4003	Long-term sexual function in survivors of vulvar cancer: a cross-sectional study.	Female Sexual Function Index, SF36, Body Image Scale, Life Orientation Test	No	Survivors	All	120	Primary
3852	Development of a postsurgical patient-reported outcome instrument for women with vulvar neoplasia.	WOMAN-PRO	No	All	All	10	Secondary
3720	A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study.	WOMAN-PRO	No	All	Surgery	65	Secondary

3131	Impact of radical operative treatment on the quality of life in women with vulvar cancer--a retrospective study.	EORTC QLQ-C30	No	All	Surgical	199	Primary
2377	The impact of surgery for vulval cancer upon health-related quality of life and pelvic floor outcomes during the first year of treatment: a longitudinal, mixed methods study.	EORTC QLQ-C30, SF-36, electronic Pelvic Floor Assessment Questionnaire	No	All	All	23	Primary
1982	Perceived Health-Related Quality of Life in Women With Vulvar Neoplasia: A Cross Sectional Study.	SF-36, WOMAN-PRO	No	All	Surgical	65	Primary

Appendix IV: Detailed search strategies developed for a systematic review of measurement properties according to published CONsensus-based Standards for the selection of health Measurement INstrument guidelines.

("gynaecological cancer" OR "gynae cancer" OR "gynecological cancer" OR "gyne cancer" OR "endometrial neoplasms" OR "uterine cervical neoplasms" OR "genital neoplasms" OR "ovarian neoplasms") AND ("EORTC QLQ-C30" OR "EORTC Quality of Life Questionnaire- Core Questionnaire" OR "EORTC QLQC30") AND (instrumentation[sh] OR methods[sh] OR "Validation Studies"[pt] OR "Comparative Study"[pt] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment (health care)"[MeSH] OR "outcome assessment"[tiab] OR "outcome measure*" [tw] OR "observer variation"[MeSH] OR "observer variation"[tiab] OR "Health Status Indicators"[Mesh] OR "reproducibility of results"[MeSH] OR reproducib*[tiab] OR "discriminant analysis"[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR "coefficient of variation"[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR "precise values"[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR "item discriminant"[tiab] OR "interscale correlation*" [tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR "minimal detectable concentration"[tiab] OR interpretab*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR "meaningful change"[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab])

N.b. The text highlighted in yellow was replaced for each included PROM and the search rerun to identify articles relevant for each instrument. The search terms developed and included for each PROM are included below:

EORTC QLQ-OV28:

("EORTC QLQ-OV28" OR "EORTC Quality of Life Questionnaire- Ovarian Cancer Module" OR "EORTC QLQOV28")

FACT-O:

("FACT-O" OR "FACT O" OR "Functional Assessment of Cancer Ovarian" OR "Functional Assessment of Cancer O" OR "FACT Ovarian")

SF-36:

("SF-36" OR "Short Form-36" OR "Short Form (36) Health Survey" OR "36-Item Short Form Questionnaire" OR "Medical Outcomes Study Questionnaire Short Form 36 Health Survey" OR "MOS SF-36")

FACT-G:

("FACT-G" OR "Functional Assessment of Cancer - General" OR "FACT G" OR "Functional Assessment of Cancer - G" OR "FACT-General")

Hospital Anxiety and Depression Scale:

("Hospital Anxiety and Depression Scale" OR "HADS")

FACT-CX:

("FACT-CX" OR "Functional Assessment of Cancer-Cervix" OR "FACT-Cervix" OR "FACT CX")

EQ-5D:

("EQ-5D" OR "EQ-5D-5L" OR "EuroQOL five dimension")

Female Sexual Function Index:

("Female Sexual Function Index" OR "FSFI")

EORTC QLQ-EN24:

("EORTC QLQ-EN24" OR "EORTC Quality of Life Questionnaire- Endometrial Cancer Module" OR "EORTC QLQEN24")

FACIT-Spiritual:

("FACIT-Sp" OR "12-item Spiritual Well-Being Scale" OR "FACIT-Sp-12" OR "Functional Assessment of Chronic Illness Therapy Spiritual Well-Being")

SF-12:

("SF-12" OR "12-Item Short Form Survey" OR "SF12" OR "Short Form Health Survey")

WOMAN-PRO:

("WOMAN-PRO" OR "WOMAN-PRO Instrument")

Impact of Event Scale:

("Impact of Events Scale" OR "Impact of Events Scale-Revised" OR "IES" OR "IES-R")

Measure of Ovarian Symptoms and Treatment:

("Measure of Ovarian Symptoms and Treatment" OR "MOST")

FACT-GOG-Ntx:

("FACT-GOG-Ntx" OR "FACT/GOG-Ntx" OR "Ntx Subscale")

Brief Pain Inventory:

("Brief Pain Inventory" OR "BPI" OR "Brief Pain Inventory- Short Form" OR "BPI-sf")

Life Orientation Test:

("Life Orientation Test" OR "Life Orientation Test- Revised" OR "LOT" OR "LOT-R")

State-Trait Anxiety Inventory:

("State Trait Anxiety Inventory" OR "STAI" OR "State-Trait Anxiety Inventory")

Appendix V: COSMIN Risk of Bias checklist and template to report methodological quality of individual studies of measurement properties.

Table 4: Risk of Bias checklist for structural validity.

Structural Validity					
Does the study concern unidimensionality or structural validity? ²	unidimensionality / structural validity				
<i>Statistical Methods</i>	very good	adequate	doubtful	inadequate	NA
For CTT: Was exploratory or confirmatory factor analysis performed?	Confirmatory factor analysis performed	Exploratory factor analysis performed		No exploratory or confirmatory factor analysis performed	Not applicable
For IRT/Rasch: does the chosen model fit to the research question?	Chosen model fits well to the research question	Assumable that the chosen model fits well to the research question	Doubtful If the chosen model fits well to the research question	Chosen model does not fit to the research question	Not applicable

Was the sample size included in the analysis adequate?	FA: 7 times the number of items and ≥ 100	FA: at least 5 times the number of items and ≥ 100 , OR at least 6 times number of items but < 100	FA: 5 times the number of items but < 100	FA: < 5 times the number of items	
	Rasch/IPL models: ≥ 200 subjects	Rasch/IPL models: 100-199 subjects	Rasch/IPL models: 50-99 subjects	Rasch/IPL models: < 50 subjects	
	2PL parametric IRT models OR Mokken scale analysis: ≥ 1000 subjects	2PL parametric IRT models OR Mokken scale analysis: 500-999 subjects	2PL parametric IRT models OR Mokken scale analysis: 250-499 subjects	2PL parametric IRT models OR Mokken scale analysis: < 250 subjects	
<i>Other</i> Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws (e.g., rotation method not described)	Other important methodological flaws (e.g., inappropriate rotation method).	

Table 5: Risk of Bias checklist for internal consistency.

Internal consistency					
Does the scale consist of effect indicators, Le. Is it based on a reflective model? ¹	yes / no				
<i>Design requirements</i>	very good	adequate	doubtful	Inadequate	NA
Was an internal consistency statistic calculated for each unidimensional scale or subscale separately?	Internal consistency statistic calculated for each unidimensional scale or subscale		Unclear whether scale or sub scale is unidimensional	Internal consistency statistic NOT calculated for each unidimensional scale or sub scale	
<i>Statistical methods</i>					
For continuous scores: Was Cronbach's alpha or omega calculated?	Cronbach's alpha, or Omega calculated		Only item-total correlations calculated	No Cronbach's alpha and no item-total correlations calculated	Not applicable
For dichotomous scores: Was Cronbach's alpha or KR-20 calculated?	Cronbach's alpha or KR-20 calculated		Only item-total correlations calculated	No Cronbach's alpha or KR-20 and no item-total correlations calculated	Not applicable
For IRT-based scores: Was standard error of the theta (SE (0)) or reliability coefficient of estimated latent trait value (index of (subject or item) separation) calculated?	SE(0) or reliability coefficient calculated			SE(0) or reliability coefficient NOT calculated	Not applicable
<i>Other</i>					

Were there any other Important flaws In the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

¹ If the scale is not based on a reflective model, internal consistency is not relevant

Table 6: Risk of Bias checklist for Cross-cultural validity\Measurement Invariance.

Cross-cultural validity\Measurement invariance					
<i>Design requirements</i>	very good	adequate	doubtful	inadequate	NA
Were the samples similar for relevant characteristics except for the group variable?	Evidence provided that samples were similar for relevant characteristics except group variable	Stated (but no evidence provided) that samples were relevant characteristics except group variable	Unclear whether samples were similar for relevant characteristics except group variable	Samples were NOT similar for relevant characteristics except group variable	
<i>Statistical methods</i>					
Was an appropriate approach used to analyse the data?	A widely recognised or well justified approach was used	Assumable that the approach was appropriate, but not clearly described	Not clear what approach was used or doubtful whether the approach was appropriate	Approach not appropriate	Not applicable
Was the sample size included in the analysis adequate?	Regression analyses or IRT/Rasch based analyses: 200 subjects per group	150 subjects per group	100 subjects per group	<100 subjects per group	

	MGCFA*: 7 times the number of items and ≥ 100	5 times the number of items and ≥ 100 , OR 5-7 times the number of items but < 100	5 times the number of items but < 100	< 5 times the number of items	
<i>Other</i>					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

*MGCFA: multi-group confirmatory factor analyses

Table 7: Risk of Bias checklist for reliability.

Reliability					
Design requirements	very good	adequate	doubtful	inadequate	NA
Were patients stable in the interim period on the construct to be measured?	Evidence provided that patients were stable	Assumable that patients were stable	Unclear if patients were stable	Patients were NOT stable	
Was the time interval appropriate?	Time interval appropriate		Doubtful whether time interval was appropriate or time interval was not stated	Time interval NOT appropriate	
Were the test conditions similar for the measurements? e.g. type of administration, environment, instructions	Test conditions were similar (evidence provided)	Assumable that test conditions were similar	Unclear if test conditions were similar	Test conditions were NOT similar	
Statistical Methods					

For continuous scores: Was an intraclass correlation coefficient (ICC) calculated?	ICC calculated and model or formula of the ICC is described	ICC calculated but model or formula of the ICC not described or not optimal. Pearson or Spearman correlation coefficient calculated with evidence provided that no systematic change has occurred	Pearson or Spearman correlation coefficient calculated WITHOUT evidence provided that no systematic change has occurred or WITH evidence that systematic change has occurred	No ICC or Pearson or Spearman correlations calculated	Not applicable
For dichotomous/nominal/ordinal scores: Was kappa calculated?	Kappa calculated			No kappa calculated	Not applicable
For ordinal scores: Was a weighted kappa calculated?	Weighted Kappa calculated		Unweighted Kappa calculated or not described		Not applicable
For ordinal scores: Was the weighting scheme described? e.g., linear, quadratic	Weighting scheme described	Weighting scheme NOT described			Not applicable
Other					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

Table 8: Risk of Bias checklist for measurement error.

Measurement Error					
Design requirements	very good	adequate	doubtful	inadequate	NA
Were patients stable in the interim period on the construct to be measured?	Patients were stable (evidence provided)	Assumable that patients were stable	Unclear if patients were stable	Patients were NOT stable	
Was the time interval appropriate?	Time interval appropriate		Doubtful whether time interval was appropriate or time interval was not stated	Time interval NOT appropriate	
Were the test conditions similar for the measurements? e.g. type of administration, environment, instructions	Test conditions were similar (evidence provided)	Assumable that test conditions were similar	Unclear if test conditions were similar	Test conditions were NOT similar	
Statistical Methods					
For continuous scores: Was the Standard Error of Measurement (SEM), Smallest Detectable Change (SDC) or Limits of Agreement (LoA) calculated?	SEM, SDC, LoA calculated	Possible to calculate LoA from the data presented		SEM calculated based on Cronbach's alpha, or on SD from another population % agreement calculated	Not applicable

For dichotomous/nominal/ordinal scores: Was the percentage (positive and negative) agreement calculated?	% positive and negative agreement calculated	% agreement calculated			Not applicable
<i>Other</i>					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

Table 9: Risk of Bias checklist for criterion validity.

Criterion validity					
	very good	adequate	doubtful	inadequate	NA
Statistical methods					
For continuous scores: were correlations, or the area under the receiver operating curve calculated?	Correlations or AUC calculated			Correlations or AUC NOT calculated	Not applicable
For dichotomous scores: were sensitivity and specificity determined?	Sensitivity and specificity calculated			Sensitivity and specificity NOT calculated	Not applicable
Other					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

Table 10: Risk of Bias checklist for hypotheses testing for construct validity

Hypotheses testing for construct validity					
Comparison with other outcome measurement instruments (convergent validity)					
	very good	adequate	doubtful	inadequate	NA
Design requirements					
Is it clear what the comparator instrument(s) measure(s)?	Constructs measured by the comparator instrument(s) is clear			Constructs measured by the comparator instrument(s) is not clear	
Were the measurement properties of the comparator instrument(s) sufficient?	Sufficient measurement properties of the comparator instrument(s) in a population similar to the study population	Sufficient measurement properties of the comparator instrument(s) but not sure if these apply to the study population	Some information on measurement properties of the comparator instrument(s) in any study population	No information on the measurement properties of the comparator instrument(s), OR evidence for insufficient measurement properties of the comparator instrument(s)	
Statistical methods					
Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
Other					

Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws (e.g., only data presented on a comparison with an instrument that measures another construct)	Other important methodological flaws	

Table 11: Risk of Bias checklist for hypotheses testing for comparison between known groups (discriminative or known-groups validity).

Hypotheses testing for construct validity					
Comparison between subgroups (discriminative or known-groups validity)					
	very good	adequate	doubtful	inadequate	NA
<i>Design requirements</i>					
Was an adequate description provided of important characteristics of the subgroups?	Adequate description of the important characteristics of the subgroups	Adequate description of most of the important characteristics of the subgroups	Poor or no description of the important characteristics of the subgroups		
<i>Statistical methods</i>					
Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
<i>Other</i>					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws (e.g., only data presented on a comparison with an instrument that measures another construct)	Other important methodological flaws	

Table 12: Risk of Bias checklist for responsiveness: criterion approach (comparison to a gold standard).

Responsiveness					
Criterion approach (i.e., comparison to a gold standard)					
	very good	adequate	doubtful	inadequate	NA
Statistical methods					
For continuous scores: were correlations between change scores, or the area under the Receiver Operator Curve (ROC) curve calculated?	Correlations or Area under the ROC Curve (AUC) calculated			Correlations or AUC NOT calculated	Not applicable
For dichotomous scales: were sensitivity and specificity (changed versus not changed) determined?	Sensitivity and specificity calculated			Sensitivity and specificity NOT calculated	Not applicable
Other					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws	Other important methodological flaws	

Table 13: Risk of Bias checklist for responsiveness: construct approach (comparison with other outcome measurements)

Responsiveness					
Construct approach - Comparison with other outcome measurement instruments					
	very good	adequate	doubtful	inadequate	NA
Design requirements					
Is it clear what the comparator instrument(s) measure(s)?	Constructs measured by the comparator instrument(s) is clear			Constructs measured by the comparator instrument(s) is not clear	
Were the measurement properties of the comparator instrument(s) sufficient?	Sufficient measurement properties of the comparator instrument(s) in a population similar to the study population	Sufficient measurement properties of the comparator instrument(s) but not sure if these apply to the study population	Some information on measurement properties of the comparator instrument(s) in any study population	No information on the measurement properties of the comparator instrument(s), OR evidence for insufficient measurement properties of the comparator instrument(s)	
Statistical methods					
Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
Other					

Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws (e.g., only data presented on a comparison with an instrument that measures another construct)	Other important methodological flaws	

Table 14: Risk of Bias checklist for responsiveness: construct approach (hypotheses testing before and after intervention)

Responsiveness					
Construct approach – hypotheses testing before and after intervention					
	very good	adequate	doubtful	inadequate	NA
<i>Design requirements</i>					
Was an adequate description provided of the intervention given	Adequate description of the intervention		Poor description of the intervention	No description of intervention	
<i>Statistical methods</i>					
Was the statistical method appropriate for the hypotheses to be tested?	Statistical method was appropriate	Assumable that statistical method was appropriate	Statistical method applied NOT optimal	Statistical method applied NOT appropriate	
<i>Other</i>					
Were there any other important flaws in the design or statistical methods of the study?	No other important methodological flaws		Other minor methodological flaws (e.g., only data presented on a comparison with an instrument that measures another construct)	Other important methodological flaws	

Appendix VI: Summary cards for each of the gynaecological PROMs assessed according to COSMIN guidelines.

Table 15: Summary card for EORTC QLQ-C30

Instrument	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Core Questionnaire
Acronym	EORTC QLQ-C30
Core Domain	Quality of Life
Area assessed (Number of questions)	30 items - 5 functional domain subscales: physical, role, emotional, cognitive and social; - 3 symptom scales: fatigue, nausea and vomiting, and pain; - 6 single item symptom items: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties; - Global Health Status/QoL
Description	Developed to assess the quality of life of cancer patients
Recall period	7 days
Scoring information	4-point Likert scale linearly transformed to 0-100 scale
Estimated completion time	< 10 minutes
Mode of administration	Self-administer
Contact and copyright information	Quality of Life Unit, EORTC Data Center Avenue, Brussels, eortc@eortc.be
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	1

Table 16: Summary card for EORTC QLQ-OV28

Instrument	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Ovarian Module
Acronym	EORTC QLQ-OV28
Core Domain	Quality of Life
Area assessed (Number of questions)	28 items Subscale domains: abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease and treatment, and sexual functioning
Description	Questionnaire module developed to be used with EORTC QLQ-C30 to measure quality of life issues in patients with ovarian cancer
Recall period	7 days
Scoring information	4-point Likert scale linearly transformed to 0-100 scale
Estimated completion time	~ 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Quality of Life Unit, EORTC Data Center Avenue, Brussels, eortc@eortc.be
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	5

Table 17: Summary card for EORTC QLQ-EN24

Instrument	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Endometrial Module
Acronym	EORTC QLQ-EN24
Core Domain	Quality of Life
Area assessed (Number of questions)	24 items Subscale domains: lymphoedema, urological symptoms, body image, sexual functioning, chemotherapy symptoms
Description	Questionnaire module developed to be used with EORTC QLQ-C30 to measure quality of life issues in patients with endometrial cancer
Recall period	7 days
Scoring information	4-point Likert scale linearly transformed to 0-100 scale
Estimated completion time	~ 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Quality of Life Unit, EORTC Data Center Avenue, Brussels, eortc@eortc.be
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	2

Table 18: Summary card for EORTC QLQ-CX24

Instrument	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Cervical Module
Acronym	EORTC QLQ-CX24
Core Domain	Quality of Life
Area assessed (Number of questions)	24 items Domains: symptom experience, body image, sexual/vaginal functioning, lymphoedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity, sexual enjoyment
Description	Questionnaire module developed to be used with EORTC QLQ-C30 to measure quality of life issues in patients with cervical cancer
Recall period	7 days
Scoring information	4-point Likert scale linearly transformed to 0-100 scale
Estimated completion time	~ 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Quality of Life Unit, EORTC Data Center Avenue, Brussels, eortc@eortc.be
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	8

Table 19: Summary card for FACT-G

Instrument	Functional Assessment of Cancer Therapy - General
Acronym	FACT-G
Core Domain	Quality of Life
Area assessed (Number of questions)	27 items Domain subscales: Physical, functional, social/family, emotional well-being
Description	Instrument developed to measure health-related quality of life in patients undergoing cancer therapy
Recall period	7 days
Scoring information	5-point Likert scale linearly transformed to 0-100 scale (subscale scores, total scores, Trial Outcome Index)
Estimated completion time	~ 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Copyright 1987, 1997. Questionnaires and all related subscales, translations, and adaptations are owned and copyrighted by David Cella.
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	2

Table 20: Summary card for FACT-O

Instrument	Functional Assessment of Cancer Therapy - Ovarian
Acronym	FACT-O
Core Domain	Quality of Life
Area assessed (Number of questions)	12 items Domains: Appearance, body image, GI symptoms, sexual items relating to interest and fertility
Description	Instrument developed to measure health-related quality of life in patients with ovarian cancer undergoing cancer therapy. FACT-O supplementary module to FACT-G questionnaire
Recall period	7 days
Scoring information	5-point Likert scale linearly transformed to 0-100 scale (subscale scores, total scores, Trial Outcome Index)
Estimated completion time	< 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Copyright 1987, 1997. Questionnaires and all related subscales, translations, and adaptations are owned and copyrighted by David Cella.
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	2

Table 21: Summary card for FACT-GOG/Ntx

Instrument	Functional Assessment of Cancer Therapy/Gynecological Oncology Group - Neurotoxicity
Acronym	FACT/GOG-Ntx
Core Domain	Quality of Life
Area assessed (Number of questions)	11 items Domains: Neurotoxicity: sensory, motor, hearing, dysfunction
Description	Provides a targeted assessment of symptoms of peripheral neuropathy in cancer patients undergoing treatment.
Recall period	7 days
Scoring information	5-point Likert scale linearly transformed to 0-100 scale (subscale scores, total scores, Trial Outcome Index)
Estimated completion time	< 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Copyright 1987, 1997. Questionnaires and all related subscales, translations, and adaptations are owned and copyrighted by David Cella.
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	4

Table 22: Summary card for FACT-CX

Instrument	Functional Assessment of Cancer Therapy - Cervical
Acronym	FACT-CX
Core Domain	Quality of Life
Area assessed (Number of questions)	15 items Domain subscales: Physical, emotional, sexual function, fertility
Description	Instrument developed to measure health-related quality of life in patients with cervical cancer undergoing cancer therapy. FACT-CX supplementary module to FACT-G questionnaire
Recall period	7 days
Scoring information	5-point Likert scale linearly transformed to 0-100 scale (subscale scores, total scores, Trial Outcome Index)
Estimated completion time	< 5 minutes
Mode of administration	Self-administer
Contact and copyright information	Copyright 1987, 1997. Questionnaires and all related subscales, translations, and adaptations are owned and copyrighted by David Cella.
Licensing and equipment cost	Free for use in academia
Number of studies evaluating instrument	3

Table 23: Summary card for EQ-5D

Instrument	EuroQol- 5 Dimension
Acronym	EQ-5D
Core Domain	Quality of Life
Area assessed (Number of questions)	6 items Domains: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression, own health.
Description	Standardised measure of health-related quality of life
Recall period	Present status
Scoring information	Includes visual analog scale (VAS) recording respondents self-rated health status on 0-100 scale. EQ-5D descriptive system comprising five dimensions of health which can be used as a health profile or converted into an index score representing a von Neumann—Morgenstern utility value for current health. Health states converted into a weighted health state index score by applying scores from the EQ-5D preference weights elicited from the general population.
Estimated completion time	~ 5 minutes
Mode of administration	Self-administer
Contact and copyright information	EuroQol Research Foundation Marten Meesweg 107 3068 AV Rotterdam The Netherlands T: +31 (0) 884400190 E: userinformationservice@euroqol.org
Licensing and equipment cost	No License Fee but must register with EuroQol for access
Number of studies evaluating instrument	2

Table 24: Summary card for MOST

Instrument	Measure of Ovarian Symptoms and Treatment
Acronym	MOST
Core Domain	Quality of Life
Area assessed (Number of questions)	24 items Domains: Pain, fatigue, abdominal bloating/discomfort, sleep disturbance, bowel disturbance, nausea and vomiting, shortness of breath, poor appetite, urinary symptoms, weight changes
Description	Instrument to measure the most prevalent symptoms in patients with recurrent ovarian cancer undergoing treatment
Recall period	4 weeks
Scoring information	0-10 numeric rating scale before rescaling to 0-100
Estimated completion time	10-15 minutes
Mode of administration	Self-administer
Contact and copyright information	Gynecologic Cancer Intergroup Symptom Benefit Study, Copyright © 2014 by IGCS and ESGO.
Licensing and equipment cost	-
Number of studies evaluating instrument	2

Table 25: Summary card for FSFI

Instrument	Female Sexual Function Index
Acronym	FSFI
Core Domain	Quality of Life
Area assessed (Number of questions)	19 items Domains: Desire, arousal, lubrication, orgasm, satisfaction, pain
Description	Instrument developed to assess six domains of female sexual function in women
Recall period	7 day
Scoring information	0-5/1-5 scoring scales (Domain scores derived from the multiplication of the sum of domain items points and the domain factor. Summation of all domains)
Estimated completion time	~15 minutes
Mode of administration	Self-administer
Contact and copyright information	Developed by Bayer AG, Zonagen, Inc. and Target Health Inc., 2000
Licensing and equipment cost	Free to use
Number of studies evaluating instrument	3

Appendix VII: Specimen of the short-form 26-item Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire, as downloaded from the source (Michigan Medicine, University of Michigan).

1. Over the past 4 weeks, how often have you leaked urine?

- More than once a day..... 1
 About once a day..... 2
 More than once a week..... 3 (Circle one number)
 About once a week..... 4
 Rarely or never..... 5

2. Which of the following best describes your urinary control during the last 4 weeks?

- No urinary control whatsoever..... 1
 Frequent dribbling..... 2 (Circle one number)
 Occasional dribbling..... 3
 Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?

- None 0
 1 pad per day..... 1
 2 pads per day..... 2 (Circle one number)
 3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you during the last 4 weeks?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding with urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Need to urinate frequently during the day.....	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you during the last 4 weeks?

- No problem..... 1
 Very small problem..... 2
 Small problem..... 3 (Circle one number)
 Moderate problem..... 4
 Big problem..... 5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	<u>No Problem</u>	<u>Very Small Problem</u>	<u>Small Problem</u>	<u>Moderate Problem</u>	<u>Big Problem</u>
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements.....	0	1	2	3	4
c. Losing control of your stools.....	0	1	2	3	4
d. Bloody stools	0	1	2	3	4
e. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

No problem.....	1	
Very small problem.....	2	
Small problem.....	3	(Circle one number)
Moderate problem.....	4	
Big problem.....	5	

8. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	<u>Very Poor to None</u>	<u>Poor</u>	<u>Fair</u>	<u>Good</u>	<u>Very Good</u>
a. Your ability to have an erection?.....	1	2	3	4	5
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections during the last 4 weeks?

None at all.....	1	
Not firm enough for any sexual activity.....	2	
Firm enough for masturbation and foreplay only.....	3	(Circle one number)
Firm enough for intercourse.....	4	

10. How would you describe the FREQUENCY of your erections during the last 4 weeks?

I NEVER had an erection when I wanted one.....	1	
I had an erection LESS THAN HALF the time I wanted one.....	2	
I had an erection ABOUT HALF the time I wanted one	3	(Circle one number)
I had an erection MORE THAN HALF the time I wanted one.....	4	
I had an erection WHENEVER I wanted one.....	5	

11. Overall, how would you rate your ability to function sexually during the last 4 weeks?

- Very poor..... 1
 Poor..... 2
 Fair..... 3 (Circle one number)
 Good..... 4
 Very good..... 5

12. Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?

- No problem..... 1
 Very small problem..... 2
 Small problem..... 3 (Circle one number)
 Moderate problem..... 4
 Big problem..... 5

13. How big a problem during the last 4 weeks, if any, has each of the following been for you?

(Circle one number on each line)

	<u>No</u> <u>Problem</u>	<u>Very Small</u> <u>Problem</u>	<u>Small</u> <u>Problem</u>	<u>Moderate</u> <u>Problem</u>	<u>Big</u> <u>Problem</u>
a. Hot flashes.....	0	1	2	3	4
b. Breast tenderness/enlargement..	0	1	2	3	4
c. Feeling depressed.....	0	1	2	3	4
d. Lack of energy.....	0	1	2	3	4
e. Change in body weight.....	0	1	2	3	4

Gaining stakeholder insight into perceived barriers and facilitators to routine collection of patient-reported outcome measures at a large NHS Cancer Centre.

GUIDE FOR SEMI-STRUCTURED INTERVIEWS

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The planned study aims to develop understanding of the need for routine collection of patient reported outcome measurements (PROMs) in cancer clinical practice. The study will gather insight from key stakeholders, including healthcare professionals and patients, about perceived barriers and facilitators to the successful implementation of PROM collection in an NHS setting.

The interview will follow a semi-structured approach and will recruit key stakeholders including healthcare professionals, support staff and patients. The interviewer is not required to strictly adhere to the structure below and may ask the outlined questions in no particular order. The interviews will take place either Guy's Hospital or virtually using the Zoom platform and should last no more than a maximum of 45 minutes per study participant.

Some questions to consider during the one-to-one interview:

The interviewer may ask the following main questions (in no particular order) and if needed, ask clarifying questions to cover a topic fully.

Main Questions
What is your understanding of a patient-reported outcome measurement (PROM)? (HCP) Do you have any experience of administrating or using PROMs? - Was this research based? Or clinical? Please expand on your experiences if applicable.
How do you feel about the routine collection of PROMs at Guy's Cancer? (Do you think there is a strong need and how essential is this for patients and clinicians) Do you know whether PROMs are already routinely collected in any tumour type or setting? Do you think this planned implementation will be effective in your setting?
What is the general level of receptivity in your department specifically to commence collecting PROMs? Do you know of any other organisations who have implemented the routine collection of PROMs within the clinical setting?
What kind of infrastructure changes would be needed to accommodate routine collection of PROMs? What sort of resources (money, training, education, physical space, time etc) would you envisage needing for collection of PROMs routinely in the clinical setting? Would any training or education be useful and improve the effectiveness of this project? Who are the key individuals to engage to ensure success of this implementation project? Are there any incentives you can think of that would help ensure the implementation is successful?
Can you think of any potential issues which would affect the success of the planned roll-out of routine implementation of PROMs? What do you think are thee most important factors (logistics wise) to ensure engagement of both patients and healthcare professionals (frequency of PROMs, timing, collection method)

Appendix IX: Evaluative questionnaire administered to patients recruited to the feasibility study developed at Guy's Cancer Centre.

Dear Mr XX XX,

Thank you for continuing to complete the EPIC-26 questionnaire after receiving external beam radiotherapy treatment for your prostate cancer at Guy's and St Thomas' NHS Foundation Trust. We would now like to ask some questions about your experience of completing this questionnaire:

1. How have you been completing the EPIC-26 questionnaires?
☐ Electronically (accessing the questionnaire through a link sent via email)
☐ On paper (posting the questionnaire back to the hospital)

Note for reviewers: if the patient chooses "Electronically" for question 1, they will complete questions 2-4. If the patient selects "On paper", they complete questions 5-6. All patients complete question 7 onwards.

2. If you completed the questionnaire electronically, which device did you use to access it?
☐ Computer or laptop
☐ Tablet
☐ Mobile phone

3. How easy was it to **access** the REDCap platform to complete the questionnaire electronically?

1 (Very difficult)	2	3	4	5 (Very easy)

4. How easy was it to **use** the REDCap platform to complete the questionnaire?

1 (Very difficult)	2	3	4	5 (Very easy)

5. If you completed the questionnaire on paper, please indicate why this method was preferable to electronic completion:

6. Did you experience any issues with returning your completed questionnaire, if sending via post?
☐ Yes
☐ No
☐ Don't know

- a. If you experienced issues with returning your completed questionnaire, please describe in detail:

7. Did you experience any difficulties with completing the EPIC-26 questionnaire?

- ☐ Yes
☐ No
☐ Don't know

- a. Please describe any difficulties you experienced with completing the EPIC-26 questionnaire:

8. If you experienced any difficulties, would you know who to contact to get help with completing the questionnaire?

- ☐ Yes
☐ No
☐ Don't know

9. Which electronic method for accessing the EPIC-26 questionnaire do you prefer?

- ☐ Via an email link
☐ Via a text message
☐ Via a downloadable app
☐ No method would be convenient

10. How understandable were the questions in the EPIC-26 questionnaire?

1 (Very difficult to understand)	2	3	4	5 (Very easy to understand)

11. How long on average did it take you to complete the EPIC-26 questionnaire?

12. Was the amount of time it took to complete the EPIC-26 questionnaire acceptable to you?

1 (Very unacceptable)	2	3	4	5 (Very acceptable)

13. The EPIC-26 questionnaire is being completed by you at the following timepoints:

- Before finishing radiotherapy
- 6-weeks post radiotherapy
- 3-months post radiotherapy
- 6-months post radiotherapy
- 12-months post radiotherapy
- 18-months post radiotherapy
- 24-months post radiotherapy.

What is your opinion on the number of times you are being asked to complete the questionnaire?

1 (Too many times)	2	3	4	5 (Not enough times)

14. What do you think about the schedule of completing the questionnaire?

1 (Too much time in between questionnaires)	2	3	4	5 (Too little time in between questionnaires)

15. How frequently is the maximum you would be happy to complete the EPIC-26 questionnaire?

- ☐ Weekly
- ☐ Fortnightly
- ☐ Monthly
- ☐ 3-monthly
- ☐ 6-monthly
- ☐ Annually
- ☐ Other

If Other, please specify below:

16. Did you complete the EPIC-26 questionnaire fully at each timepoint?

- ☐ Yes
- ☐ No
- ☐ Don't know

a. If no, are you aware of which timepoints you did not fully complete the EPIC-26 questionnaire?

17. Please describe any reasons as to why the questionnaire was either: (a) not fully completed, or (b) not completed at each timepoint

18. Did you receive any information about the EPIC-26 questionnaire (what it is, why it is important etc) from any of the clinical team looking after you?

- ☐ Yes
☐ No
☐ Don't know

- a. Who provided you with information about the EPIC-26 questionnaire?

- ☐ Consultant
☐ Nurse
☐ Radiographer
☐ Researcher
☐ Other

If other, please specify below:

19. Do you think that an education tool explaining these patient questionnaires (including why they are important, how they are used) would be useful both for yourself and other patients?

- ☐ Yes
☐ No
☐ Don't know

- a. If yes, what sort of educational tool would be most useful to you?

- ☐ Online video
☐ Website
☐ Leaflet or Explanatory Note
☐ Poster in hospital
☐ Other

20. Can you think of any incentives, or rewards, which might help ensure all patients complete every questionnaire?

21. Are you aware of whether the EPIC-26 questionnaire has been used to help with your care?

- ☐ Yes
☐ No
☐ Unsure

22. Do you think regularly completing the EPIC-26 questionnaire has impacted your care at all (either positively or negatively)?

- ☐ Yes – improved my care
☐ Yes – negatively affected my experience
☐ No – no change to care
☐ Don't know

23. How helpful has the EPIC-26 questionnaire been for describing your symptoms and quality of life after radiotherapy treatment?

1 (Very unhelpful)	2	3	4	5 (Very helpful)

24. Please include any further comments or feedback you may have about the content of the EPIC-26 questionnaire and your experience of completing it:

25. Based on your experience of completing the EPIC-26 questionnaire, how likely are you to complete future questionnaires related to your cancer care?

1 (Very unlikely)	2	3	4	5 (Very likely)