The Burden of Barrett's Oesophagus

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

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Abstract

The Burden of Barrett's Oesophagus

Barrett's oesophagus is a well-established and increasingly common precancerous condition which requires long term endoscopic surveillance. Undoubtedly this may impact patients both physically and psychologically. However, very little is known about the true burden of this condition and its care pathways on patients' quality of life.

This thesis presents a body of work, in journal format, which aims to give both an in-depth qualitative account of disease impact and quantitative assessment of the prevalence of these factors. Finally, this thesis identifies broader patient centred research uncertainties, which if investigated will hopefully shift the landscape of research in favour of the patient.

The chapters presented in this thesis include an introductory literature review which highlights what is currently known, limitations of research to date, and gaps in knowledge concerning BO health related quality of life. The following two chapters (chapters 2 and 3) adopt a mixed method approach (qualitative and quantitative) to assessing BO health related quality of life. These chapters address the impact of symptoms, worry of oesophageal cancer, anxiety, depression, perceptions of cancer risk, experiences of follow up care and patient views on new follow up systems. Chapter 4 then looks at the broader issues facing patients with BO and GORD by asking what are their key future research priorities. This qualitative and quantitative prioritisation process engages both patients and professionals on a level playing. This process culminates in a modified Delphi process to reach a consensus "top 10 research priorities". Chapter 5 begins to assesses the potential benefits of a dedicated BO surveillance service, a top 10 research priority identified in chapter 4. Finally, a discussion chapter brings together the key findings from all 4 journal articles before outlining future research proposals in abstract format.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

Preface

I studied undergraduate medicine at the University of Manchester, although was geographically placed at Keele University where I subsequently completed my foundation training years at The University Hospital of North Staffordshire. I soon moved to Manchester to complete my core medical training where my interest in gastroenterology bloomed. As a junior registrar I rapidly obtained a love of endoscopy and conducted a series of endoscopic performance indicator audits and small quality improvement projects. This interest of investigating and enhancing outcomes for patient benefit soon grew into a desire to pursue out of programme research. I was fortunate enough to be put in contact with Professor Ang and subsequently Professors McLaughlin and Hamdy. The initial research idea was born out of the Barrett's Oeosphagus BSG guideline future developments; i) "Better understanding of the impact of screening and surveillance on QOL" and ii) "Effects of current and future care pathways on patient QOL should be formally evaluated".

Twelve months later, in January 2016, I started my research journey as a clinical research fellow at Wrightington, Wigan and Leigh NHS Trust. I have therefore been lucky enough to experience clinical research from its very infancy to completion. This PhD has provided me vital first-hand exposure to writing a research proposal and protocol, ethics application, grant application, CRN portfolio adoption, running of a clinical trial, data analysis, manuscript preparation and the peer review process. It became clear early on that this body of work would fit nicely into a journal format thesis. The publication of my work during my PhD has really helped focus my efforts, hone my findings and delineate future ideas and concepts. This has also allowed me to present my work at a national conference and international symposium. Outside of my PhD, during this time, my family has both grown up and grown in size. I have also studied for and passed my Gastroenterology SCE (diet 2018) in preparation for completing higher training.

Acknowledgements

Statement: As the author of this thesis I can confirm I have made a significant contribution to all chapters presented.

I have been extremely fortunate to undertake this PhD in Barrett's oesophagus and I owe so much gratitude to so many people who have helped make this happen. Firstly, my main supervisor, Professor Ang, whose initial idea over a coffee in January 2015 has now become a CRN adopted study and this PhD thesis. His enthusiasm for Barrett's research is endless and somewhat infectious! He has pushed me to achieve things I would have never thought possible over the last three years, while giving me free reign to explore my own ideas and interests. Likewise, he seems to innately know when not to push too hard and appreciates, more than anyone, the importance of a work life balance, family and other interests. He has been a fantastic supervisor and now a good friend and mentor. Secondly, my co-supervisors Professor John McLaughlin and Shaheen Hamdy, throughout this process have provided me with a succinct, timely and invaluable sounding board. Their vast experience and superb guidance are unrivalled. Thirdly, I am hugely grateful to the following people for their contributions:

- Maria Horne guided me through the complex qualitative elements of this thesis (chapter 2). I will miss our skype calls and I hope we can continue to collaborate on future projects.
- Dr Kelly Chatten who helped with data analysis in chapter 5
- Dr Tom Riley who helped collect data in chapter 5
- Paraskevi Taxiarchi who helped conduct the statistical analysis in chapter 3 and Dr Glen Martin who provided further statistical support and critique in chapter 3.
- Dr Robert Willert for helping support our study at Central Manchester Foundation Trust.
- Lisa Gadeke and Professor Lawrence Lovat for their efforts as steering group members for the research priority setting exercise (chapter 4) with thanks also to Professor Chris Hawkey who co-supervised.
- Dr Richard Keld, Dr Neeraj Prasad, Dr Alastair Cairns and manager John Murry were all influential in creating, supporting and futureproofing the clinical research fellow post at Wrightington, Wigan and Leigh (WWL) NHS Trust.
- The WWL NHS Research and Development department staff who have been extremely patient and dedicated helping us bring this project to life.
- To all the participants and patient representatives, I thank you for your time and invaluable contributions.

Finally, my wife Jules has had to put up with me at home a little more! She's held our young family together when I've had to burn the midnight oil. At times when I have doubted myself, she's

snapped me out of it and often put herself last without question or hesitation. I look forward to the next chapter of this work and I hope Dr Elizabeth Ratcliffe, who now takes over the baton, has an equally fulfilling and enjoyable experience.

Alternative Thesis Format

I have been granted permission to submit this Ph.D. thesis in an alternative format by my supervisors Professors Yeng Ang, John McLaughlin and Shaheen Hamdy approved under the University of Manchester, Faculty of Medical and Human Sciences regulations. This thesis is written in the manner of an introductory literature review and research hypothesis followed by a series of chapters written as journal papers, 4 of which have been published (chapters 1,2,4 and 5). All chapters are focused around the overriding theme of Barrett's oesophagus disease burden. However, each chapter asks either a different question or adopts an alternative methodology. The journal style thesis format has facilitated timely publication throughout this PhD, the process of which has been invaluable to help refine findings and delineate future work.

Publications and Presentations related to this thesis

Publications

Chapter 1: (Published in The Lancet Gastroenterology and Hepatology)

Britton J, Keld R, Prasad N, Hamdy S, McLaughlin J, Ang Y. Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health-related quality of life. Lancet Gastroenterol Hepatol. 2018 Jan;3(1):57-65. doi: 10.1016/S2468-1253(17)30213-3. Epub 2017 Sep 29.

Chapter 2 (Published in Health Expectations)

Britton J, Hamdy S, McLaughlin J, Horne M, Ang Y. Barrett's oesophagus: A qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect. 2019 Feb;22(1):21-33. doi: 10.1111/hex.12817. Epub 2018 Nov 14.

Chapter 3 (Presented in poster format at BSG 2019)

Britton J, Taxiarchi P, Martin G, Willert R, Horne M, Hamdy S, McLaughlin J, Ang Y. A comparative qualitative survey of patient experience in Barrett's oesophagus. Abstract submitted to BSG 2019 meeting. Paper to be submitted to BMJ Gastroenterology.

Chapter 4: (Published in The Lancet Gastroenterology and Hepatology)

Britton J, Gadeke L, Lovat L, Hamdy S, Hawkey C, McLaughlin J, Ang Y. Research priority setting in Barrett's oesophagus and gastro-oesophageal reflux disease. Lancet Gastroenterol Hepatol. 2017 Nov;2(11):824-831. doi: 10.1016/S2468-1253(17)30250-9. Epub 2017 Sep 1.

Chapter 5: (Published in Frontline Gastroenterology)

Britton J, Chatten K, Riley T, Keld R, Hamdy S, McLaughlin J, Ang Y. Dedicated service improves the accuracy of Barrett's oesophagus surveillance: a prospective comparative cohort study. Frontline Gastroenterology 2019;10:128-134.

Presentations

Oral presentations

1) Workshop for patient representatives and professionals; "An Introduction to research priority setting. The 10th National Barrett's Oesophagus symposium (April 2016).

2) Research priority setting in Barrett's oesophagus and gastroesophageal reflux disease. International Oesophageal Cancer Symposium, Cambridge (April 2017).

Poster Presentations

1) Barrett's oesophagus: a qualitative study of patient burden and follow up needs. BSG June 2018.

2) A dedicated service improves the accuracy of Barrett's oesophagus surveillance: a prospective comparative cohort study. BSG June 2018.

3) A comparative qualitative survey of patient experience in Barrett's oesophagus. BSG June 2019.

Prizes and Awards

1) Highly Commended Award for Outstanding Contribution to Patient and Public Involvement and Engagement 2019. Faculty of Biology, Medicine and Health at The University of Manchester. Based on the work conducted in Chapter 4 of this thesis; "Research priority setting in Barrett's oesophagus and gastroesophageal reflux disease".

3) Best presentation in the category of oesophageal posters at the BSG 2019. Based on the work conducted in chapter 3; "A comparative qualitative survey of patient experience in Barrett's oesophagus" PTU-048.

List of Abstracts

Chapter 1; Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health-related quality of life.

Barrett's oesophagus is a chronic precancerous condition that predisposes patients to the development of oesophageal adenocarcinoma, which, once invasive, carries a poor prognosis. This likelihood of a negative outcome has led to the development of robust surveillance and treatment pathways. The true effect of Barrett's oesophagus on life expectancy and the efficacy of long-term surveillance remains under debate. With these uncertainties and more accurate methods of individual risk stratification yet to reach routine clinical practice, patients must be continually monitored and thus carry the burden of this chronic disease. In this Review, we summarise the major findings concerning the patients' perspective of this disease and its care pathways. Health-related quality of life (HRQoL) measurement has become a valuable metric to assess the effects of disease, the quality of health-care delivery, and treatment efficacy across various disease settings. Research to date has shown significant reductions in HRQoL scores related to Barrett's oesophagus compared with controls from the general population. The scores of patients with Barrett's oesophagus seem to be similar to those of patients with gastro-oesophageal reflux disease. Symptom control appears to be important, but not the only factor, in maximising HRQoL. Most researchers have used generic and disease-specific HRQoL instruments because there are few outcome measures that are validated and reliable in patients with Barrett's oesophagus. These methodologies potentially overlook crucial unmeasured areas that are specific to patients with Barrett's oesophagus. Historically, follow-up care has left some patients with insufficient understanding of the disease, inaccurate perceptions of cancer risk, and an unnecessary psychological burden. A greater understanding of the prevalence of these factors and identification of follow-up needs specific to these patients will help to shape future health-care delivery and improve patient experience

Chapter 2; Barrett's oesophagus: A qualitative study of patient burden, care delivery experience and follow-up needs.

Introduction: Barrett's oesophagus (BO), a precursor to oesophageal adenocarcinoma, requires long term endoscopic surveillance. The rising incidence of this chronic disease has implications for service provision and patient burden. Few studies have explored BO patients' personal burden, care delivery experience and participation in healthcare delivery decisions. This study aimed to

identify and explore factors impacting on BO patients' health-related quality of life, follow up needs and views on new models of follow up care.

Methods: An exploratory qualitative approach was adopted using semi-structured, in-depth one-to-one interviews; audio recorded and transcribed verbatim. Patients undergoing BO surveillance, at a single NHS Hospital, were recruited using purposive sampling with the aim of achieving maximum variation. Data were analysed using Framework analysis approach, supported by NVivo Pro 11.

Results: Data saturation occurred after 20 participant interviews. Ten subthemes and 3 main themes emerged from analysis: 1) Burden of disease – symptom control, worry of oesophageal cancer and surveillance endoscopy; 2) Follow up experiences – follow up care, at this NHS hospital, was found to be inconsistent and often inadequate to meet patients' needs. In particular, a lack of disease specific information; 3) Follow up needs – participants sought enhanced communication, organisation and structure of care. They highly valued face to face interaction with a specialist and the concept of direct secondary care access in-between endoscopies was reassuring to participants.

Conclusion: This qualitative research provides an in-depth account of the patients' perspective of BO, the effectiveness of follow up care and patient opinion on new follow up systems.

Chapter 3; A comparative quantitative survey of patient experience in Barrett's oesophagus

Introduction: This study aimed to assess Health Related Quality of Life (HRQoL) in patients with non-dysplastic Barrett's oesophagus (NDBO) and endoscopically treated dysplastic Barrett's oesophagus (DBO).

Methods: This quantitative, self-administered questionnaire study was conducted across three NHS hospitals. Data was also collected from two other cohorts; GORD/dyspepsia and colonic polyp surveillance individuals. HRQoL measurement included the Short Form-36 (SF-36), Gastrointestinal Symptom Rating Scale (GSRS), Hospital Anxiety and Depression Scale (HADS) and the Cancer Worry Scale (CWS). Fisher's exact and Spearman's rank correlation tests were used for analysis alongside propensity score matching to adjust for age, sex and comorbidities.

Results: 686 participants responded to the survey (response rate 39%), of which 639 were eligible for analysis (NDBO n= 306, DBO n= 49, GORD/dyspepsia n= 132, Colonic polyps n= 152). 53% of NDBO participants reported significant cancer worry comparable to those treated for DBO (50%, p=0.933) and those undergoing colonic polyp surveillance (51%, p=0.355). Significantly less cancer specific worry was reported in GORD/dyspepsia participants (43.4%, p=0.01). NDBO participants reported anxiety in 15.8% (n=48) and depression in 8.6% of cases which was statistically comparable

to the other cohorts. Moderate-severe heartburn or acid regurgitation was found in 11% and 10% respectively in the NDBO cohort. This was comparable to the DBO cohort (heartburn 2% p=0.172, acid regurgitation 4% p=0.31) but significantly lower (better) than GORD/dyspepsia participants (heartburn 31% p=<0.001, acid regurgitation 25% p=0.001). NDBO participants with moderate/severe GORD symptoms were associated with higher rates of anxiety (p=<0.001), depression (p=<0.001) and cancer specific worry (p=<0.001). Those who correctly perceived their cancer risk as low tended to have significantly lower rates of cancer worry (p=<0.001).

Conclusions: This study provides a valuable insight into the problems BO patients may face. Based on these findings future care pathways must be more patient focused with greater reassurance and communication to address misconceptions of cancer risk, oesophageal cancer related worry and GORD symptom control.

Chapter 4; Research Priority Setting in Barrett's Oesophagus and Gastroesophageal Reflux Disease

Introduction: The incidence of gastro-oesophageal reflux disease and Barrett's oesophagus is increasing. Barrett's oesophagus is the main precursor to oesophageal adenocarcinoma, which has a poor prognosis. In view of the vast potential burden of these diseases on patients and health-care resources, there is a real need to define and focus research efforts. This priority setting exercise aimed to produce a list of the top ten uncertainties in the field that reflect the priorities of patients and health-care providers.

Methods: We adopted the robust and transparent methodologies previously outlined by the James Lind Alliance. This qualitative approach firstly involves an idea gathering survey that, once distilled, generates a longlist of research uncertainties. These uncertainties are then prioritised via an interim ranking survey and a final workshop to achieve consensus agreement.

Results: The initial 629 uncertainties, generated from a survey of 170 individual respondents (47% professional, 53% non-professional) and one workshop, were narrowed down to the final top ten uncertainties of priority for future research. These priorities covered a range of issues, including a need for improved patient risk stratification, alternative diagnostic and surveillance tests, efficacy of a dedicated service for Barrett's oesophagus, cost-effectiveness and appropriateness of current surveillance, advances in development of non-drug treatments for gastro-oesophageal reflux disease, safety of long-term drug treatment, and questions regarding the durability and role of different endoscopic therapies for dysplastic Barrett's oesophagus.

Conclusion: This is the first patient-centred assessment of priorities for researchers in this chronic disease setting. We hope that recognition and dissemination of these results will shape the future direction of research and translate into meaningful gains for patients.

Chapter 5; Dedicated service improves the accuracy of Barrett's oesophagus surveillance: a prospective comparative cohort study

Introduction: Standards for Barrett's oesophagus (BO) surveillance in the UK are outlined in the British Society of Gastroenterology (BSG) guidelines. This study aimed to assess the quality of current surveillance delivery compared to a dedicated service.

Methods: All patients undergoing BO surveillance between January 2016 and July 2017 at a single NHS district general hospital were included. Patients had their endoscopy routed to a dedicated BO endoscopy list or a generic service list. Prospective data were analysed against the BSG guidelines and also compared to each patient's prior surveillance endoscopy.

Results: 361 patients were scheduled for surveillance of which 217 attended the dedicated list, 78 attended the non-dedicated list and 66 did not have their endoscopy. The dedicated list adhered more closely to the BSG guidelines when compared to the non-dedicated and prior endoscopy respectively; Prague classification (100% vs 87.3% vs 82.5%, $p<0.0001$), hiatus hernia delineation (100% vs 64.8% vs 63.3%, $p<0.0001$), location and number of biopsies recorded (99.5% vs 5.6% vs 6.9%, $p<0.0001$), Seattle protocol adherence (72% vs 42% vs 50%, $p<0.0001$) and surveillance interval adherence (dedicated 100% vs prior endoscopy 75%, $p<0.0001$). Histology results from the dedicated and non-dedicated list cohorts revealed similar rates of intestinal metaplasia (79.8% vs 73.1%, $p=0.12$) and dysplasia/OAC (4.3% vs 2.6%, $p=0.41$).

Conclusion: The post-BSG guideline era of BO surveillance remains suboptimal in this UK hospital setting. A dedicated service appears to improve the accuracy and consistency of surveillance care, although the clinical significance of this remains to be determined.

1. Chapter 1 - Introduction and Literature Review

1.1. Introduction

Barrett's oesophagus (BO) has been defined as "an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (>1cm) above the gastro-oesophageal junction and confirmed histopathologically from oesophageal biopsies" (1). It predisposes to the development of oesophageal adenocarcinoma (OAC) which, once invasive, carries a poor prognosis (<13% overall survival at 5 years) (2,3). Research assessing the true prevalence is somewhat limited by the need for invasive endoscopy to diagnose it. Two European studies have reported a general population prevalence of 1.3% and 1.6% (4,5). A recent meta-analysis demonstrated a 0.33% annual cancer conversion rate from non-dysplastic Barrett's to OAC (6). This risk is similar to that reported in first degree relatives of BRCA 1/2 mutation carriers with breast cancer (7,8). Current evidence, albeit from retrospective cohort and comparative studies suggests that surveillance correlates with earlier staging and improved survival from cancer (9-15). This has led to the development of robust surveillance guidelines and more recently clear treatment pathways both in Europe and the United States (1,2,16). Although surveillance is widely practiced there remains no randomized control trial (RCT) demonstrating its efficacy. The cost effectiveness of surveillance versus no surveillance for BO is somewhat unclear with the decisive RCT Barrett's Oesophagus Surveillance Study (BOSS) expected to be completed in the near future (17). The majority of cost effective studies conducted comparing BO surveillance versus no surveillance found that surveillance was dominated by no surveillance (i.e. not cost effective) or had a cost-effective ratio greater than accepted thresholds (18-21). However, the cost-effectiveness of endoscopic therapy for dysplastic BO versus surveillance versus surgery is less disputed with a number of studies finding it superior (22-26). In the interim, patients and physicians continue to carry out surveillance and treatment pathways with very limited data or knowledge regarding the patient's perspective. What is the impact on patient's health related quality of life (HRQOL), psychological well-being and perceived cancer risk? What issues really matter to patients on a day to day basis? And are patients' priorities reflected by the focus of current research or does a significant gap between the researcher and research user exist?

This literature review will summarise existing knowledge concerning the patients' perspective of BO. Significant limitations, areas of debate and gaps in the current evidence base will be discussed. The review has been divided into 3 main areas;

1. Measuring Health Related Quality of Life in chronic disease.
    - Identify and describe the various approaches and tools used by researchers in quality of life (QOL) measurement.

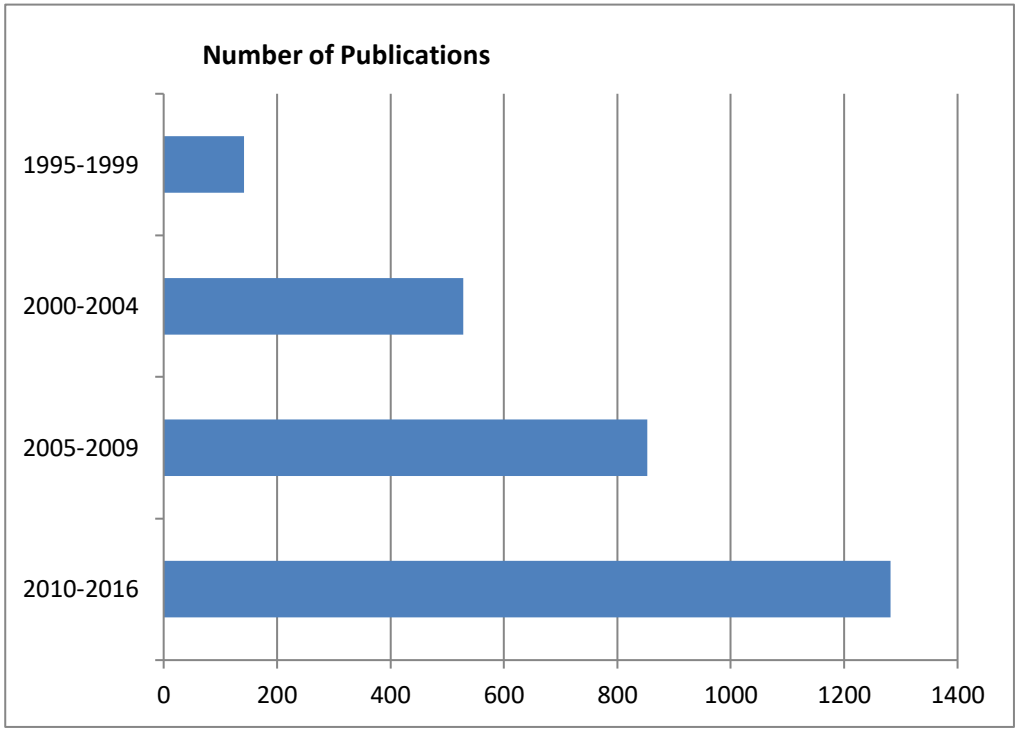
2. Health Related Quality of Life in Barrett's Oesophagus
    - Highlight the major findings and concepts already published regarding the impact of BO on HRQOL.
    - Consider other factors not assessed by traditional HRQOL measurement. For example, the burden of endoscopy, worry of cancer and psychological distress.
3. Patient and Public Involvement (PPI) in Research and Healthcare Improvement Strategies.
    - Discuss the role and methods of PPI in both research and healthcare improvement strategies. We will also consider how PPI could be used in the setting of BO, particularly helping identify the key issues for patients.

Relevant articles were identified by an advanced PubMed search using "Barrett's Oesophagus" (including the spelling "esophagus") alongside the following terms; "Quality of life", "Health related Quality of Life", "HRQOL", "Worry of Cancer", "Burden", "Health State Utilities", "Patient Reported Outcomes", "Patient and Public Involvement (PPI)", "Research Priority Setting". Bibliographies of any relevant papers were also scrutinised including review articles and letters to the editor.

1.2. Why Measure Health Related Quality of Life?

"HRQOL reflects physical, social and emotional attitudes and behaviours of an individual as they relate to their prior and current health state" (27). Historically clinical outcomes have been assessed with objective measures such as mortality, length of hospital stay and laboratory markers. These measures do not necessarily correlate with patients' subjective well-being. A number of chronic diseases, including BO, have inadequate or expensive objective measures for example oesophageal ph-studies, manometry and gastroscopy. Due to the limitations of such measures researchers and clinicians have designed tools to subjectively measure QOL. (28) described 3 main uses of HRQOL assessment; I) "Descriptive" to measure and compare aspects of HRQOL in multiple disease states. II) "Discriminative" to differentiate subgroups within a disease, for example crohns disease patients typically display worse QOL than Ulcerative colitis in cohorts of Inflammatory bowel disease patients. III) "Evaluative" to help assess treatment efficacy or the quality of health care delivery. The need to use QOL as an outcome measure continues to grow and is reflected by a sustained rise in the number of publications concerning "gastroenterology and quality of life" over the past 15 years (the concept of figure 1.2-1 was originally reported by Borgaonkar in 2002 (29)).

Figure 1.2-1. The number of Pubmed publications concerning "gastroenterology" and "quality of life" over time.



1.3. How is Health Related Quality of Life Measured

Traditionally HRQOL has been assessed using stand alone or combinations of global, generic and disease specific instruments. In order to develop a reliable assessment tool a number of key psychometric properties must be considered (29-31) (table 1.3-1)

Table 1.3.1 Key Psychometric Properties in devloping a reliable assessment tool

Property	Definition	Method of Assessment
Validity		
• Face	Measures what it is supposed to	Literature review, expert opinion, patient input
• Content	Samples the most important areas	Pre-testing with item reduction/augmentation
• Construct	Relationship between the score and a hypothesis of what is been measured	Compared to another marker of illness.
• Criterion (convergent)	Relationship with a validated questionnaire	Comparison to an accepted well validated instrument
• Discriminative	Can distinguish between 2 groups of dissimilar patients	Scores for patients with different disease severity should be significantly different
Reliability		
• Test-retest	Ratio between patient variation to total variation in score	Similar scores when repeated in similar/identical situations. Interclass correlation coefficient (ICC) 0-1 (1 perfect agreement)
• Internal Consistency	Correlation with items in the same domain or with the total score	Cronbach's alpha coefficient 0-1 (1 excellent)
Responsiveness	Able to detect change over time	Clinically important change overtime should be reflected in the QOL scores
Other Important Properties	Self-Administered Adequate recall period Adequate comprehension	

1.3.1. Global Instruments

Global assessments represent rudimentary summaries of overall function. They are quick and easy to perform but are unable to identify specific areas of dysfunction (27). They may often overlook small but significant changes. Typical global assessment tools include the 10cm Visual Analogue Scale (VAS), the Graded Scale (5-point Likert scale ranging from excellent-extremely poor) and Health State Utility scores. The latter has more relevance and implications in economic cost-effective studies.

1.3.2. Generic Instruments

Generic instruments (e.g. the Short Form 36) are multi-item questionnaires which assess aspects of general health and well-being. They are likely to detect significant impacts of a disease. Considering their generic construct, they have been used across disease groups to provide valuable comparisons. Table 1.3.2-1 summarises the key generic instruments, their uses and limitations (32-36). For years these questionnaires were used in isolation and represented a seemingly comprehensive QOL assessment in the majority of publications and clinical trials. However used as standalone assessments clinically important disease specific dysfunctions may go unrecognised

(30). This led to the development of hybrid and disease specific instruments which are often used alongside generic scores in HRQOL measurement.

Table 1.3.2-1 Generic Instruments

Instrument Author	Items Domains	Domains	Administered	Recall period	Advantages/Uses	Limitations
Short Form-36 (SF-36) (35)	36/8	Physical and Psychological; physical functioning, role limitations, bodily pain, general health, vitality, social functioning, role limitations-emotional, mental health	Self-administered	Past 4 weeks	The most extensively used and validated generic QOL measure	Complex to administer and score. May miss important disease specific change.
Psychological General Well-Being (PGWB) index (36)	22/6	General health, positive well-being, self-control, vitality, depression, anxiety	Self-administered or Interview	Past 1 month	Extensively used and validated.	Complex to administer and score. May miss important disease specific change. Focuses on psychological wellbeing, important domains are not covered e.g. physical functioning.
Sickness Impact Profile (SIP) (32)	136/12	Physical (ambulation, mobility, body care and movement) Psychological (social interaction, alertness and emotional behavior) communication, sleep and rest, eating, work, home management, recreation and pastimes.	Self-administered	Not specified	Extensively used, detects changes over time, allows comparisons among diseases/populations.	May not detect significant QOL differences among populations or diseases with minimal disease burden due to ceiling effects. Complex and timely to administer. May miss important disease specific change.
Nottingham Health Profile (NHP) (33)	38/6	Energy level, Emotional reactions, physical mobility, pain, social isolation, sleep	Self-administered	Not specified	Simple to administer	Ceiling effects similar to SIP, limited responsiveness. May miss important disease specific change
EQ-5D (34)	5 Domains	Mobility, self-care, usual activities, pain and discomfort, anxiety and depression. 3 or 5 point Likert (severity scale) with a VAS.	Self-administered	Past 12 months	Health economic calculations. NICE recommended for health state utility assessment. Quick and easy to administer	Reasons for reduced QOL may not be apparent. Unable to detect disease specific problems.

Medical Outcomes Study Short-Form 36 (SF-36)

The SF-36 is the only generic score used in the both BO and Gastro-oesophageal reflux disease (GORD). It was originally developed for the Medical Outcomes Study in 1992 (35) and has remained the most widely used and validated generic QOL scoring measure. The 36-item score is subdivided into eight domains; physical functioning, role limitations, bodily pain, general health, vitality, social functioning, role limitations-emotional and mental health. Summary mental and physical scores can also be calculated. Total scores range from 0-100 with higher scores indicating better QOL. Abbreviated versions were also developed (SF-20 and SF-12). The SF-12 only gives physical and mental summary scores rather than individual domains. The reliability and validity of these condensed versions are significantly lower than the full SF-36 but are superior to global single item measurements such at the VAS (37). Despite its widespread usage, a number of GI diseases exhibit particular aspects which cannot be detected using the SF-36 alone. In a study of IBS patients clinically important factors concerning upper gastrointestinal symptoms, musculoskeletal symptoms, sleep and sexual dysfunction went unrecognised (38).

1.3.3. Hybrid Instruments

These instruments have borrowed elements of the generic questionnaires and combined them with domains designed to assess symptoms. None of these instruments, designed specifically for GORD, have been used in a BO cohort. Table 1.3.3-1 summarises the components of each score, their uses and significant limitations (39-41).

Table 1.3.3-1 Hybrid Instruments

Instrument	Items/Domains	Domains	Administered	Recall Period	Uses	Limitations
Domestic/International Gastroenterology Surveillance Study (DIGEST) (39)	Part 1; 27 item questionnaire with 3 Domains assessing 14 GI symptoms Part 2; Generic PGWB index.	Severity, frequency and impact on daily activities	Interview	3 Months	Developed to assess the prevalence of GI disease and the impact of symptoms on HRQOL. Good internal consistency and reliability.	Timely and impractical for routine clinical use.
The Reflux Questionnaire (40)	31 items 7 Domains	Heartburn, acid reflux, wind, eating, swallowing, bowel movements, sleep, work, physical, social activities	Self-administered	2 Weeks	Developed to evaluate GORD symptoms, HRQOL and economic data in surgical vs medically treated groups.	Imbalanced focus on symptoms (5/7 domains) with key HRQOL domains missing (e.g. mental health)
HRQOL in individuals with GORD (41)	57 items 8 Domains (2 from the generic SF-12 and 6 disease specific domains)	Physical and mental summary scores alongside eating symptoms, social restriction, sleep, work and treatment satisfaction	Self-administered	Past 4-8 weeks	Measure HRQOL in symptomatic non-erosive GORD patients	Poorly validated

1.3.4. Disease Specific Instruments

More recently HRQOL researchers have chosen to use a generic QOL tool (i.e. the SF-36) alongside a disease specific score. A number of gastrointestinal specific and GORD specific instruments have been created in an attempt to identify the particular nuances of the target condition. To our knowledge there is no validated disease specific score pertaining to non-dysplastic BO. All scoring systems used to assess BO populations have been either generic, designed for GORD or a combination of both. Table 1.2.4-1 and 1.2.4-2 summarises the uses and limitations of these disease specific instruments (42-50). Table 1.2.4-3 highlights the psychometric properties of each score.

Table 1.3.4-1 Gastrointestinal Disease Specific Instruments

Gastrointestinal Specific Instruments						
Instrument	**Items Domains**	**Domains**	**Administered**	**Recall Period**	**Advantages/Uses**	**Limitations**
Gastrointestinal Symptom Rating Scale (GSRS) (42)	15 items 5 Domains	Abdominal pain, reflux, indigestion, diarrhea, constipation	Self-administered	Past week	Extensively used symptom specific score measuring frequency, intensity, duration and impact on daily life. Can measure clinically important change and discriminates well between the domains, most markedly in the reflux domain.	Inadequate overall HRQOL assessment when used alone. Poor discrimination in the constipation domain.
Gastrointestinal Quality of Life Index (GIQLI) (43)	36 items 5 Domains	Core Symptoms, physical, psychological, social, disease specific	Self-administered	Past 2 weeks	Measure QOL in a number of GI specific disease. Showed good responsiveness in pre and post treatment groups (laparoscopic fundoplication)	Cannot discriminate between GI diseases, more than half the items relate to symptom frequency. Timely to administer
Patient Assessment of upper Gastrointestinal disorders (PAGI-QOL) (47)	30 items 5 Domains	Daily activities, clothing, diet and food habits, relationship, psychological well-being and distress	Self-administered or Interview	Past 2 weeks	Measure of HRQOL in upper GI disorders. Good discrimination when comparing patients according to symptom severity and level of daily activities	Not clear if it can discriminate between different GI diseases. Minimal use/publications.
Quality of Life in Reflux and Dyspepsia (QOLRAD) (50)	25 items 5 Domains	Emotional stress, sleep disturbance, food and drink, physical and social functioning, vitality	Self-administered	Past week	Assess HRQOL in reflux and dyspepsia. Extensively used in trials. Good validity and reliability.	Timely to administer

Red Highlighted Scores have been used in BO

Table 1.3.4-2 GORD Disease Specific Instruments

Gastro-Esophageal Reflux Disease Health Related Quality of Life (GERD-HRQOL) (45)	10 items	6 Heartburn symptoms, 2 dysphagia/odynophagia, 1 impact of medication, 1 overall satisfaction	Self-administered	Not specified	Measure of symptom severity	Poor validity and reliability
Quality of life questionnaire in Gastroesophageal reflux (Reflux-Qual and short-form Reflux-Qual (RQS) (44, 46)	37 items The Short Form version (RQS) has 8 items (mean score x 25= full score)	Daily life, well-being, psychological impact, seep and eating	Self-administered	Past 4 weeks	Evaluate HRQOL in GORD patients. Reflects frequency and severity well and detects changes over time.	Mainly validated in the French version only.
Quality of Life in Anti-Reflux Surgery (QOLARS) (48)	45 items pre-surgery 50 items post-surgery	Combination of the EORTC-QLQ-C30, Visick score and modified GERD-HRQOL	Self-administered	Not specified	Designed specifically for GORD surgical patients with pre and post questionnaires.	Timely to administer. EORTC-QLQ-C30, Visick scores are well validated and accepted instruments. The modified GERD-HRQOL component is poorly validated.
Heartburn Quality of Life Questionnaire (HBQOL) (49)	15 items	Role physical, pain, sleep, diet, social, mental health	Self-administered	Past week and past 30 days	Developed to detect changes in QOL before and after GORD treatment.	Minimal use since initial validation.

Red Highlighted Scores have been used in BO

Table 1.3.4-3 The Psychometric Properties of Gastrointestinal and GORD Disease Specific Instruments.

Instrument	Validity			Reliability	
	Face	**Content**	**Construct**	**Internal Consistency Cronbach's alpha coefficient**	**Test-retest interclass coefficient**
GSRS	L, E	Factor analysis	SF-36, PGWB	0.6-0.85	0.42-0.6
GIQLI	E, PI	Factor analysis	Spitzer quality of life index, Bradburn Affect Balance Scale	>0.90	0.92
PAGI-QOL	NS	NS	SF-36	0.83-0.96	All aspects >0.70 (excluding the relationship scale 0.61)
QOLRAD	L, E, PI	Factor Analysis	SF-36 GSRS	0.88-0.97 (for single dimensions) 0.97-0.99 (for total score)	0.65-76 (GORD cohort)
GERD-HRQOL	E	NT	Poor correlation with SF-36	NT	NT
RQS	E	NS	SF 12	0.84	NT
QOLARS (modified GERD-HRQL component)	E	NT	Visick Score	>0.70	NT
HBQOL	L, E	NT	SF-36	0.75-0.91	NT

L= Literature Review, E= Expert Opinion, PI= Patient Interviews, NT= Not Tested, NS= Not Specified. Red Highlighted Scores have been used in BO

Barrett's Oesophagus Disease Specific QOL Instrument

Only one study to date has designed a QOL measure specifically for BO patients. This tool was developed to assess the patient impact during the Ablation of Intestinal Metaplasia containing Dysplasia Trial (AIM trial) (51). It constitutes 10 items including 2 yes or no questions and 8 visual analogue scales relating to worry, depression, QOL, stress and impact on daily living including sleep. Although the qualitative research methodology used to develop the score infers good content validity this instrument remains invalidated with no reliability data. Visual analogue scales can also be subject to ceiling effects. Considering the questionnaire was designed specifically for dysplastic BO patients it cannot be used reliably in non-dysplastic cohorts. In particular, key areas such as symptom control are absent. Nevertheless, it highlights important issues for all Barrett's patients

which more generic scoring systems may overlook such as such as cancer worry and psychological burden.

1.4. Health Related Quality of Life in Barrett's Oesophagus.

HRQOL has been extensively evaluated in GORD. Few studies, particularly in Europe and the UK, have attempted to assess HRQOL in Barrett's Oesophagus. The majority of researchers have used a combination of generic and disease specific instruments. Eloubeidi first assessed Barrett's patients in 1997 and again in 2000 (52). Age and gender matched US veterans with BO or GORD were compared to previously published general population controls. Both groups demonstrated similar reductions in HRQOL compared to the general population. Heightened severity and frequency of symptoms (GERD questionnaire) appeared to correlate with greater bodily pain and reduced social functioning subdomains on the SF-36 form. Without controlling for symptom severity, it is unclear from this study whether reductions in HRQOL in BO patients were driven by symptoms or other aspects. Despite good response rates this study was also underpowered with <100 participants per group.

More recently Lippmann and colleagues (53) prospectively examined HRQOL in BO (n=168), erosive GORD (72) and non-erosive GORD (n=289) in a US tertiary centre. The SF-36 was again used to generate generic QOL data alongside a widely used measure of psychological distress (The Revised Hopkins Symptom Checklist 90 or SCL-90-R). GORD and gastrointestinal specific instruments included the GERD-HRQOL and GIQLI questionnaires. All three groups, demonstrated significant reductions in all aspects of the SF-36 compared to previously published general population controls. Overall scores were comparable to studies of patients with diabetes and clinical depression. BO patients had better physical component summary scores and more favourable scores in the bodily pain, vitality and role limitations-emotional subdomains. BO participants also demonstrated better symptom control and greater overall disease/GI specific QOL scores compared to both GORD groups. This finding is perhaps expected as other studies have shown BO patients experience fewer reflux symptoms than GORD sufferers (5,54). Interestingly this observation remained after adjusting for symptom severity. No significant differences between the groups were found in the psychological assessment scores. This study suggests HRQOL losses in BO are not as severe as those seen in GORD groups. QOL reductions, from this evidence, appear to be associated with physical symptoms causing impaired functioning rather than significant psychological impacts. Although this study provides valuable insights into QOL in BO it has significant limitations in its design. All patients were recruited from a single tertiary centre hence patients with GORD, particularly non-erosive disease, probably don't reflect the vast majority of GORD patients in a primary care setting. It is likely this subgroup may have a significant functional component to their disease with heightened

symptom perception. Participants were also recruited from endoscopy which itself can acutely impact both physical and psychological scores giving a false impression of the participant's true background state. One other explanation for BO cohorts reporting better symptom control than GORD groups may be the difference between measuring prevalent cases (usually BO) against incident cases (usually GORD). Indeed, when incident cases alone have been directly compared the 2 groups symptoms were comparable (55).

The study which best illustrates the importance of symptom control on QOL was part of the European ProGERD initiative. This multicentre prospective cohort study is the largest published cohort concerning BO QOL measures. It was designed to assess the impact of GORD and treatment with esomeprazole on QOL (55). Baseline HRQOL assessment (SF-36, QOLRAD and RDQ) occurred off PPI before diagnostic endoscopy. Overall scores were reduced compared to pre-published general population controls and were comparable to conditions with much greater associated mortality and morbidity such as acute coronary syndrome (56,57). After 2 weeks PPI treatment all patients QOL improved significantly (SF-36 mean PCS 43-49 and MCS 45-50). These post treatment scores probably reflect a more typical GORD population than those published by Lippmann's tertiary centre study. This is demonstrated by significantly higher mean PCS scores (49) compared to Lippmann's group (40.6) of whom 94% were also on PPI. This study clearly demonstrates the importance of symptom control in maximising patients QOL. This study has successfully shown there is perhaps a clinical role for QOL scoring to demonstrate treatment efficacy. Particularly as objective measures and questioning symptoms alone does not reflect patients' subjective well-being. However, the time constraints of these 3 questionnaires would be impractical in routine clinical use. The author goes onto suggest that HRQOL measured 2 weeks after endoscopy was not influenced by the diagnosis including those diagnosed with BO. Evidently this is an unfair assessment of a chronic disease. Firstly, all patients diagnosed with BO in this cohort presented with GORD and hence had very similar symptomology at baseline, so one would expect a similar initial QOL score. Secondly the acute impact of endoscopy must be considered when interpreting these scores. Thirdly a QOL assessment 2 weeks after diagnosis will not reflect the full impact or burden of disease.

BO encompasses much more than reflux symptom control. Particularly the worry of cancer, psychological impact and burden of repeated surveillance endoscopies. Despite their various limitations these studies have all demonstrated significant reductions in generic, disease and GI specific QOL scores in BO. We know symptom control is an important factor, however other unmeasured contributing factors may have been overlooked in this research.

One study which has attempted to identify other factors was conducted in the UK. 151 NHS patients undergoing BO surveillance completed the SF-36, Hospital anxiety and depression score (HADS),

trust in physician score (TIPS) alongside a knowledge based questionnaire (58). Again, overall SF 36 mean general health scores (mean 53.9) were reduced compared to general population (mean 70) pre-published controls. In contrast to the other studies discussed this data suggested decrements in BO QOL were worse than previously UK published reflux oesophagitis cohorts (mean 62.5). Cooper demonstrated a significant minority of participants who exhibited heightened anxiety had greater concerns of developing cancer and poorer trust in physician scores. The doctor-patient relationship appeared to have a strong influencing role in this setting. Participants with greater TIPS correlated with superior generic QOL measures in 6 out of 8 SF-36 domains. These patients also reported to have received adequate information and better disease understanding. Patients were adjusted for age, sex and socioeconomics but not co-morbidities. Another limitation to this study is the lack of a symptom severity score and the use of an invalidated knowledge-based questionnaire. It has however drawn attention to key, previously unmeasured, factors. One would expect these factors to play a crucial role in patients with chronic disease and cancer risk. Further research is needed to fully assess the prevalence of these factors and the true impact of poor knowledge, patient-physician relationships, perceived cancer risk and psychological burden. These factors may be modifiable by assessing patients follow up needs and ensuring adequate patient education. Table 1.4-1 summarises the major publications concerning QOL and BO (52,53,55,58,59).

Table 1.4-1 Summary of Barrett's Oesophagus HRQOL Studies

Author, Date, Population	Groups	Number	Instrument Generic	Scores	Instrument Specific	Scores
Eloubeidi MA 2000, US Single center (52)	BO GORD General Population	<107 <104 Pre-Published	SF-36 (median general health domain)	35 (20–60) 40 (20–62) 67 (50–82)	GERD Questionnaire	Duration (>10yr) GORD 35% BO 34% Frequency (>once/wk) GORD 57% BO 67% Severity (mod/severe) GORD 82% BO 65% Night symptoms GORD 81% BO 61%
Kulig 2003, ProGERD Initiative Multicenter ; Germany, Austria, Switzerland (55)	BO GORD (erosive) GORD (non-erosive) All participants	702 2660 2853	Pre-Treatment SF36 (PCS/MCS) Pre-Post PPI PCS Pre-Post PPI MCS	42.6/46.2 43.1/45.0 43.5/43.9 43-49 45-50	QOLRAD (Pre/Post Treatment)	4.6-6.2
Lippmann 2009, US Tertiary single center (53)	GORD (non-erosive) GORD (erosive) BO	289 72 168	SF36 (PCS/MCS) SCL-90-R	40.0/48.3 40.1/48.5 41.8/51.7 58.0 58.0 56.4	GERD-HRQOL GIQLI	18.0 15.9 13.7 124.3 131.0 137.2
Cooper 2009, UK Cross sectional, single center (58)	BO General Population Heart Failure Reflux oesophagitis BO BO	151 3850 426 101	SF-36 HADS (anxiety) HADS (depression) TIPS	53.9 70.0 46.8 62.5 6.1 (SD 4,2) 14% Abnormal 25% Borderline 61% Normal 4.0 (SD 3.5) 3% Abnormal 11% Borderline 86% Normal 44 (mean) 80% "favorable or very favorable"	NT	NT
Crockett 2012, US Cross sectional, multicenter (59)	Over surveillance (BO >1 endoscopy in 3yrs) Under surveillance (BO <1 endoscopy in 3yrs)	102 54	SF-36 PCS/MCS	47.0/50.9 44.8/49.8	GERD-HRQOL	7.8 9.1

1.5. The Burden of Endoscopy

The short term impact of cancer screening and surveillance on QOL is well documented (60). One of the main patient burdens of such tests are false positive results leading to further, often invasive, investigations and more aggressive surveillance intervals. The over diagnosis rate in mammography breast cancer screening is approximately 10% (61). In comparison the false positive rates of adenocarcinoma or high grade dysplasia in BO patients is very low (6). Low grade dysplasia (LGD) poses more of a diagnostic challenge with 73% of patients ultimately being down staged (62,63). However, this subgroup only represents a minority of patients. More concerning perhaps is the over diagnosis of BO itself and inappropriate enrolment into surveillance. On a retrospective review, by 3 endoscopists, the diagnosis of BO was refuted in 32% of patients undergoing surveillance (64). This highlights the importance of a concrete initial diagnosis, adequate sampling (65) and informed decision making of both patient and physician. Latest guidance from the British Society of Gastroenterology has recognised this and now recommends all new patients attend an outpatient clinic to review the diagnosis and discuss the role of surveillance (1)

Unlike other cancers the screening and surveillance gold standard test for BO is quite invasive. Although gastroscopy with Seattle biopsy protocol has been shown to be very safe (65) the procedure is not accepted by all patients. Kruijshaar (66) studied 180 BO patients undergoing surveillance. 59% of participants found the test “burdensome” with a significant number experiencing pain (14%) and throat ache (47%) post procedure. A comparative group of GORD patients found the test even more onerous which probably reflects the benefits of past exposure to endoscopy in BO participants, most of whom had had 2 previous endoscopies. HADS scores were significantly lower the week after endoscopy compared to before. This may not only reflect anxiety concerning the physical implications of the test but also worry of cancer and the subsequent relief from a negative test. Indeed, those who interpreted their risk of cancer to be high had higher levels of procedural discomfort and found it “burdensome”. The acute physical stresses of gastroscopy are hard to modify and perhaps what is more important are patients background levels of anxiety, depression and worry of cancer in-between endoscopies and the implications these factors have patients’ lives day to day.

1.6. Perceived Cancer Risk and Worry

Worry is a cognitive activity where an individual experiences a series of negative thoughts about an uncertain issue (67). The severity and frequency of worry appear to be the most important factors (68). Jensen and colleagues (69) examined the validity of cancer worry scales used in clinical practice and research settings. Again, severity and frequency seemed to have the strongest convergent, divergent and predictive validity. Table 1.6-1 summarises 10 measures of cancer worry used in clinical or research settings (70-79).

Table 1.6-1 Measures of Cancer Worry

Worry Measure	**Items/Likert**	**Reliability**		**Notes**
		Internal Consistency (Cronbach's alpha co-efficient)	**Test-retest (interclass coefficient)**	
Penn State Worry (72)	16/5	0.93	0.92	A generic worry score, not specific to cancer
Worry Domains (75)	25/5	0.85-0.88	0.79	A generic worry score assessing relationships, self-confidence, the future, work, finances. Not specific to cancer
Worry Severity (74)	8/4	0.86-0.91	NT	Measures general worry severity
McCaul brief worry scale (77)	3/5	0.78 (0.82 if the frequency item is removed)	NT	Designed to measure frequency and severity of worry regarding CRC. Well-designed but invalidated.
Brief worry scale (73)	4/7	0.95	NT	Developed for worry about physical health related to smoking but can be modified to cancer. A reliable measure of worry severity
Worry Chart (71)	1/5	NT	NT	A single item measure of worry severity.
Revised impact of events scale (70)	7/4	0.86	0.87	Well validated measure of the frequency of intrusive and worrisome thoughts not severity.
Champion breast cancer fear scale (78)	8/5	0.91	NT	Measures components of worry or an individual's response to worry. It can be modified to other cancers. It does not measure worry frequency or severity.
Lerman breast cancer worry scale 76)	3 items 5 or 4 Likert	Whole scale 0.57 2 Worry Impact items 0.83	NT	Assesses worry severity and the impact of worry on mood and daily functioning. Demonstrates better reliability as a 2 item worry impact score. Can be modified to other cancers.
The Cancer Worry Scale (79)	8 or 6 Items 4 Likert	0.88	NT	Used to assess fear of developing cancer or cancer recurrence in both breast, ovarian and bowel cancer. {Custers:2013jx} {Custers:2015jh}

NT= Not Tested

Worry can be situational, i.e. triggered by an event such as an endoscopy appointment, or a chronic background state called dispositional or trait based worry (80). This can be about life in general or a specific issue such as cancer. Newly diagnosed cancer patients expectantly experience significant worry (state-based cancer worry). Individuals without cancer can also dwell on this diagnosis (trait-based cancer worry). Past studies have shown trait based worry significantly influences patient behaviour in a cancer setting, for example interest in breast cancer prevention surgery among high-risk women (81).

Misperceptions of cancer risk may therefore have important psychological consequences and impact on health behaviour. Inaccurate overestimation and underestimation of breast cancer is linked to individuals worry of cancer and impacts decision making regarding surveillance and treatment (82). Appropriate counselling of patients at risk from breast cancer has been shown to reduce worry of cancer in those who overestimated their risk (83). Conversely improved patient knowledge in inflammatory bowel disease has been shown to impact negatively on QOL (84). Shaheen et al demonstrated ineffective communication with patients during their follow up of treated dysplastic BO patients. They found 41% of patients misclassified their current disease state despite a recent clinic appointment (85). This is even more surprising in a clinical trial setting conducted within tertiary specialist centres. Patient education or counselling are interventions with potential positive and negative impacts on patient's beliefs, attitudes and future health behaviour. Such interventions must be carefully considered and ideally involve patients in their design. Again, the role and influence of an effective physician-patient relationship must not be overlooked. Particularly as the majority of patients in this study overestimated their disease state.

Risk perception can be assessed numerically (absolute and relative risk) or subjectively. Patients subjective perceived risk of cancer has been shown to influence health behaviour more than their knowledge of numerical risk (82,86,87). Shaheen and colleagues (88) first reported BO patient's perceived risk of cancer using a visual analogue scale to assess numerical risk. 68% of patients undergoing surveillance (n=92) overestimated their 1-year risk of cancer (mean 13.6%). Despite this finding attendance for endoscopy and physician visits were comparable between over and under estimators. Subsequently, Kruijshaar (89) reported 63% of BO patients (n= 192) underestimated their numerical risk of OAC. These studies appear to contradict each other, however both studies used different response scales. Shaheen's VAS ranged from 0-100% with a magnified lower end of the scale whereas Kruijshaar used 7 response categories from 0.1%-10%. The upper limits of these scales are likely to blame for the over and under estimations described. Both studies, however, clearly demonstrate patient knowledge regarding numerical risk is poor and did not appear to influence health behaviour. Nevertheless, the majority of patients selected the lower end of each scale suggesting they perceive their risk as low. Kruijshaar simultaneously assessed subjective estimations of risk and found 63% of patients correctly perceived their risk as "low" or "very low".

Despite this finding adherence to surveillance was reported as high. These studies raise important questions. Are patients with BO truly provided with enough information concerning their diagnosis, role of surveillance and cancer risk? Are patients making fully informed decisions or are they just following physician advice?

Crockett and colleagues (59) tried to identify factors associated with over surveillance, present in 65% of patients with BO, in a multicentre US study. Interestingly no patient factors including; age, gender, symptom severity, anxiety or altered risk perception were linked to more frequent endoscopies. However, non-validated instruments were used to assess symptoms, anxiety and worry. These negative findings suggest physicians may be to blame for over surveillance. Poorly informed patients by overcautious physicians, are perhaps more likely to follow physician advice than play an active role in their own healthcare decisions. Endoscopist fear of medico legal liability may play a significant role in this private healthcare setting. Indeed, private health insurance was directly associated with over surveillance

1.7. The Psychological Burden

Rather than assessing risk perception some researchers have tried to measure the potential psychological consequences of living with BO. Validated scoring systems including the Revised Hopkins Symptom Checklist 90 (SCL-90-R) and the Hospital Anxiety and Depression Score have both been used in this setting (table 1.7-1) (90-94). Lippmann et al 2009, found patients with BO demonstrated worse depression sub scores (SCL-90-R) compared to GORD patients (53) . However, the global severity index scores were comparable in both groups. As discussed previously, this cohort of GORD patients are probably contaminated with a disproportionate amount of functional oesophageal disease and therefore offer a poor comparison. This is reflected by higher somatization scores in the non-erosive GORD patients. Lippmann ultimately concluded that reductions in HRQOL in BO were due to physical symptoms rather than psychological burden. These results must be viewed cautiously considering the relative instability of the SCL-90R dimension scores, multiple testing issues and single tertiary centre data.

Further studies using the HADS contradict Lippmann's conclusions. Essink-Bot et al 2007 (95), examined the burden of endoscopy in BO, oesophageal cancer and symptomatic patients undergoing gastroscopy. Anxiety scores in BO participants remained significantly raised compared to a general population control even 1 month after endoscopy. This finding suggests a heightened background state of psychological impairment rather than the acute stress of endoscopy. Both Cooper et al (58) and Kruijshaar et al (66) also reported a significant minority of patients with BO experienced anxiety which appeared to link to heightened perceived cancer risk.

Table 1.7-1 Measures of Psychological Burden

Instrument	Items/Likert	Domains	Outcome Measures	Notes
The Revised Hopkins Symptom Checklist 90 (SCL-90-R) (90)	90/4	Somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychosis (9)	Global severity index, positive symptom distress index and a positive symptom total.	Reliable and valid measurement. Self-administered. Multiple items make it timely to use (12-15mins) in clinical practice or in a research setting requiring multiple simultaneous measurements. Limited use in BO (1 study).
Hospital Anxiety and Depression Score (HADS) (91)	14/ 4	Anxiety, Depression (2)	Total scores for both Anxiety and Depression 0-7= Normal 8-10= Borderline 11-21= Abnormal	Well validated and extensively used screening tool (93,94). Including use in cancer patients (92). Self-administered and short questionnaire (2-5mins).

1.8. The Impact of Dysplasia and its Care Pathways

Until recent developments in endoscopic therapy patients with high grade dysplasia often underwent surgical oesophagectomy. Quality of life following oesophagectomy for dysplastic BO has been assessed retrospectively 5 years post-surgery. 3 studies (96-98) all found similar SF-36 scores to age and gender matched general population controls. However only Chang et al (89) used a disease specific score and demonstrated a significant prevalence of troublesome symptoms (59% had reflux or regurgitation, 55% diarrhoea, 45% bloating, 28% nausea, 28% dysphagia, 17% postprandial diaphoresis, 17% abdominal pain and 7% hoarseness). Shaheen and colleagues (85) was the first to describe QOL following radiofrequency ablation (RFA) for dysplastic BO. This assessment was conducted as part of the multi centre AIM dysplasia trial (51). Participants who had undergone RFA demonstrated reduced worry, lower depression scores and reduced impact on daily living compared to those who had undergone a sham procedure. QOL endpoints were particularly improved in those with complete eradication of both dysplasia and BO at their 12 months follow

up. Interestingly at the time of this study the true benefits of RFA were unclear. Logically, informing patients they no longer have dysplasia or indeed BO appears to influence perceived cancer risk and impact positively on QOL.

Minimally invasive, oesophageal sparing treatment for dysplasia and early OAC clearly has its benefits, particularly in terms of procedural risk and long-term symptomology. Despite this the risk of disease recurrence and burden of subsequent surveillance must not be forgotten. Current guidelines advocate 3 monthly endoscopies for the first year post endoscopic therapy (99). Although disease free rates post endoscopic treatment are improving (100), there remains a risk of intestinal metaplasia, dysplasia or OAC recurrence (101). Rosmolen et al 2010 (102) demonstrated greater fear of recurrence in early stage oesophageal cancers that were treated endoscopically compared to those who underwent oesophagectomy. Contradictory to this study, in 2010, Schembre reported no significant change in SF-36 and GIQLI scores between endoscopic and surgically treated patients (103). Although this study was grossly underpowered and retrospective in design it does raise the question of the longer-term impact, particularly once patients have survived and fully adjusted to life post-surgery.

1.9. Patient and Public Involvement in Research and Healthcare Improvement Strategies.

Assessing HRQOL and other disease specific impacts does not reflect the whole story when one contemplates the patients' perspective. With people in Britain living on average 6-8 years longer now than in 1980 (104) the burden of chronic disease on both patients and healthcare resources has never been greater. This has led to more emphasis on the role of patients in the long-term management of their own health. For example, self-care and shared decision making in Inflammatory bowel disease (105,106). Over the years this patient and professional collaboration has extended beyond decisions regarding an individual's care to encompass collective decision making in the broader arena of healthcare and research (table 1.9-1) (107-121).

Table 1.9-1 Examples of Patient Involvement in Healthcare

Example (reference)	Summary	Level of Involvement
Improving outpatient services: the Southampton IBD virtual clinic. (114)	This is a successful example of innovative self-care and patient empowerment with an alternative means of chronic disease monitoring and follow up.	Self-Care (personal impact)
Involving patients in clinical decisions: impact of an interactive video program on use of back surgery (113) Development and evaluation of a breast cancer prevention decision aid for higher-risk women (120) Empowerment of men newly diagnosed with prostate cancer. (110) Implementing shared decision making in the NHS (109) UK government, Department of Health Equity and excellence: liberating the NHS (121)	Effective shared decision-making using decision aids. Effective shared decision-making using decision aids. Effective shared decision-making using decision aids. Advice and guidance on implementing shared decision making within the NHS UK Department of Health Policy Document. "No decision about me, without me"	Shared Decision Making (personal impact)
National Institute for Health and Care Excellence (NICE) (117) Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument (107, 111) The Guideline International Network Patient and Public Involvement Working Group (112, 115)	NICE is dedicated to Improving health and social care through the development of evidence-based guidance. They have a clear patient and public involvement policy and a track record of public involvement since 1999. This enterprise has developed an appraisal tool assessing the quality of clinical practice guidelines. Within this tool is a domain evaluating "stakeholder involvement". They now have refences in >600 articles and >10,000 registered users. This working group of researchers, professionals and consumers aims to "promote ways to inform and involve the public in clinical guideline activity around the world"	Clinical Guideline Development (population/public impact)
Involving patients in setting priorities for healthcare improvement: a cluster randomized trial. (108) Public participation in health care priority setting: A scoping review. (119) UK government, Department of Health Equity and excellence: liberating the NHS (121)	This RCT demonstrated a significant influence of public involvement on the final priorities set compared to professional only groups. Differing opinions between professionals and public members lead to agreeable compromise and common ground. Review article of public involvement in healthcare priority setting and resource allocation. This review demonstrates a wide range practices when involving the public with a lack of evidence of the best methods and impact of such involvement. Government Policy regarding the patient and public voice at a local and national level ("HealthWatch England")	Health Governance (population/public impact)
The James Lind Alliance (118)	A non-profit organisation which aims to narrow the gap between the researcher and research user. Patients play a fundamental role throughout this research priority setting process in order to identify a "Top 10" list of uncertainties.	Research Priority Setting (population/public impact)
Optimizing patient involvement in quality improvement (116)	Describes three case studies of patient involvement strategies in the context of quality improvement within healthcare.	Quality Assessment and Reporting (population/public impact)

The adjunct of patient and public involvement (PPI) in research processes is increasing. Historically PPI in this arena has been hap hazard with varying degrees and stages of involvement (122). Despite this, positive impacts of PPI can be seen in all stages of the research process, particularly in ensuring appropriateness and relevance for patients (123). Nevertheless, where, when and how to involve patients in healthcare and research decision making remains somewhat uncertain. What theories and evidence underpin this process? Can public participants legitimately speak on behalf of the wider population? And is public involvement at this level truly effective or merely false piety?

1.9.1. Theoretical Constructs and Methodologies

A number of existing theories attempt to describe the internal processes which constitute public involvement in broader, non-personal, healthcare decisions. Deliberative theories have been strongly linked. This theory hypothesises that "the exchange of reasonable and credible arguments should result in mutual learning and in the generation of solutions that can be rationally justified to those affected by it" (124). Central to this definition is the way in which participants exchange information. The information exchanged must be credible and the collaborating group should focus on the potential outcomes of the discussion not just the issues raised during it (124,125). Fearon highlights the potential benefits of such an interaction (126,127):

1) Allows the sharing of views and their intensities at a level that cannot be readily achieved by a vote.
2) Generate and consider a wider range of options or ideas that may have never been considered.
3) Support and encourage more public focused proposals
4) Increase the legitimacy of the final decisions
5) Enhance the moral and intellectual properties of the participants

Although deliberative methodologies have become the crux of public participation within healthcare, there are some uncertainties and scepticism. From a democratic perspective one may dismiss deliberative methods due to an unbalanced representation of the broader public (127-129). This is supported by more recent evidence which suggests current PPI methods are tokenistic with narrow and exclusive approaches which may suffocate any meaningful contributions (130,131). Conversely a "truly reflective" public participant group where all group members are able to effectively contribute is perhaps an unrealistic goal. Unsurprisingly some researchers have therefore cast doubt on the ability of public members to actually influence professionals, hospital trust agendas and managers decisions (132,133). Perhaps higher professional hierarchal status causing greater power imbalances also contributes to this effect (134). Considering these factors, recent investigators have recommended a greater focus and investment in supporting the public in

their role. Such processes help empower public participants to legitimately speak for all, irrespective of the specific makeup of the group (124). This is supported by Brett who also identified a need to improve training, PPI procedures and professional attitudes to enhance patients impact (123).

Collins and Evans (135) described PPI impact according to participants level of experience or expertise. They suggested an intermediate level interactional expertise was important for successful deliberation. In more specifically defined domains, such as a chronic disease, the highest level of public expertise may be advantageous to provide a more contributory role. On the contrary the lowest level of experience and expertise may lead to an ineffective dialogue with professionals. Although they did not define what "expertise" encompasses, one should consider the expected level of patient involvement when designing models of PPI and recruiting patients. This notion reflects the importance of balancing power differences outlined in deliberative theories.

Although PPI has become commonplace, predominantly involving deliberative methodologies, there is no true consensus on how best to carry out this theory or indeed whether these public contributions are truly effective, particularly in the long term. Without improved consistency in reporting outcomes this will remain unanswered (123)

Boivin et al 2014 (108), was the first to try and scientifically assess the effectiveness of public involvement in collective decision making at a public level. This cluster randomised trial involved patients in setting priorities for healthcare improvement. They demonstrated mutual influence occurred between patients and professionals with both groups able to move their priorities towards the other. Although this research clearly showed patient involvement influences healthcare priorities, when compared to the professional only groups, one cannot extrapolate this into actual changes on the ground. Further analysis of this trial examined which "key ingredients" helped facilitate effective PPI (124). These factors are grounded in the theories and processes outlined previously by Martin (134):

1) *Legitimacy (*their ability to speak on behalf of other affected healthcare users). Rather than concentrating on the descriptive demographic of public participants and whether they reflect the wider population this study stressed the importance of focusing more on how public involvement strategies can help enable patient participants to legitimately speak for others.
2) *Credibility (*their ability to contribute effective and pertinent information). Public interventions must provide enough information for public participants to understand professionals and support their ability to become a valuable information source. This credibility comes partly from their own experiences and partly from having access to wider population based data.

3) *Power (*their ability to actually influence professional collaborators). This public participation process moderated power differences in a number of ways. For example, establishing common ground rules, considered seating plans, clear agenda setting and the opportunity for both groups to interact more socially. Power moderation was also aided by a feeling of greater credibility amongst the public participants. For example, they could support their arguments with hard data from public surveys or wider public interaction.

1.9.2. Research Priority Setting

Perhaps the greatest impact PPI can have on research is at the most primitive level. By helping identify what needs researching in the first instance patients can influence the future direction of research in their favour. Tallon and colleagues (136) were the first to emphasise a need for PPI in these processes. They highlighted a misfocus of osteoarthritis research on drug therapies compared to a clear need for non-drug treatments identified by patients, carers and frontline staff (GP's, rheumatologists and physiotherapists). Subsequently we have seen the development and publication of research priority setting exercises. The James Lind Alliance has published over 40 papers in different diseases and healthcare settings (118). This non-profit making organisation describes robust, clear and reproducible methodologies which have now been recognised by the national institute of health research (137,138). The impact of these priority setting exercises can be difficult to measure, particularly the longer-term wider population benefits. However publication and dissemination of "Top 10 Research Priorities" has successfully influenced the immediate direction of research (108,139) and uncovered areas previously not considered (140). To date no patient centred focus for future research exists in BO or indeed GORD. These conditions effect vast and increasing numbers of patients who are cared for by numerous frontline staff (GP's, Pharmacists, Gastroenterologists, Gastrointestinal Surgeons and endoscopy staff). Therefore, the potential impact of a priority setting exercise here is magnified.

1.10. Discussion

A single centre UK study, reporting 30 years of experience (n=1239), suggested overall mortality in BO was directly linked to excessive deaths from OAC (141). However, the true impact of Barrett's Oesophagus on life expectancy remains somewhat unclear. Retrospective evidence has demonstrated a significantly higher all-cause mortality compared to matched general population controls. However the annual mortality from OAC in this study was low (0.14% per year and 2% 10yr risk) (142) suggesting other more prevalent diseases. Indeed, 2 meta-analyses, have shown the rate of death from OAC is low compared to respiratory, cardiovascular disease and other malignancies (6,143). These studies suggest OAC is an uncommon cause of death in BO irrespective of surveillance. Despite this knowledge, BO remains the only precursor of this aggressive cancer

which once advanced carries a poor prognosis. Undeniably, cohort studies do suggest surveillance detects OAC and dysplasia at an earlier stage and subsequently improves cancer survivorship. These studies are, unfortunately, subject to lead and length time bias. Until the completion of RCT's or improved individual risk stratification methods, all patients with BO will continue with surveillance and carry the burden of this diagnosis.

Considering these doubts in the evidence base patients must be given the opportunity to discuss their diagnosis. Only then can they make fully informed decisions regarding future surveillance, lifestyle measures and treatment. Only in the recent past have the BSG recommended a formal clinic appointment for all new Barrett's diagnoses (1). Consequently, the majority of patients undergoing surveillance are likely to have been informed of their condition during a brief interaction post endoscopy. Historically this lack of emphasis on Barrett's Oesophagus may reflect physician belief or knowledge in the current evidence base (144) which in turn may even negatively impact on the quality of surveillance.

Despite all these uncertainties the patient's perspective and potential impact on their lives must not be overlooked. Quality of life measurement is a valuable tool to assess impact of disease, health care delivery and treatment efficacy. Nevertheless, it remains a difficult research endpoint to evaluate when compared to mortality or length of hospital stay for instance. Research to date has demonstrated significant reductions in Barrett's Oesophagus HRQOL scores when compared to general population controls. The scores are perhaps comparable to patients with GORD and better than those diagnosed with dysplasia. Adequate symptom control appears to be important, but not the whole story, in maximizing QOL. The majority of researchers, have used both generic (i.e. the SF-36) alongside disease specific (GORD or Gastrointestinal) scores which potentially overlook vital unmeasured areas specific to BO patients. To date there remains no validated non-dysplastic BO patient reported outcome measure.

Considering BO patients have historically not attended clinic or had the appropriate time invested at diagnosis, many are likely to have poor disease specific knowledge. It is unclear whether improved disease specific knowledge would influence health behaviour or affect QOL. One crucial component of this relates to perception of cancer risk. Assessing knowledge of numerical risk is challenging and influenced significantly by the scales used. Patient's subjective risk assessment appears a more reliable measure when assessing links to health behaviours. The association between over or under estimators of risk and subsequent psychological burden remains unclear. One would expect those who overestimate their risk to have greater worry, anxiety, depression and impaired QOL. The prevalence of these factors in BO patients undergoing surveillance is uncertain. No study has accurately assessed HRQOL alongside these factors or provided comparisons to other pre-malignant conditions requiring surveillance such as colonic adenomas.

If we can accurately identify poorly informed patients who are experiencing undue psychological distress or impaired QOL then perhaps these factors can be modified by more appropriate effective follow up techniques. Ragunath and colleagues (145) implemented a dedicated BO clinic with clear clinical benefits including discontinued surveillance in 11% and changes to anti reflux medication in 17%. Such a service could be invaluable, in a much wider sense, for both patients and physicians. It would provide an opportunity to ratify the diagnosis and assess appropriateness of further surveillance. A focused service from a more informed physician with a specialist interest may positively impact on patient education, particularly concerning cancer risk and the role of surveillance. The influence of such an intervention on patient's knowledge and QOL measures has not been assessed.

The doctor-patient relationship appears to be vitally important in shaping patients experiences and can influence future health decisions. Prior research in colonoscopy suggests recollection of the preceding procedure predicted adherence to future surveillance (146). Arney et al (147) conducted in depth qualitative interviews to highlight key areas which may influence patient's adherence to BO surveillance. They identified 6 important memories before (communication with the doctor and waiting time in the department), during (Interaction with the physician and lack of pain) and after gastroscopy (Trust and control of their BO). At least 3 of these recollections relate directly to the doctor-patient relationship, which must not be overlooked or its impact underestimated. This relationship may be strengthened by delivering a focused Barrett's service encompassing endoscopy and clinic, improving continuity of care and providing a point of contact for patients. The clinical successes and cost savings of a dedicated service are well established in other chronic diseases such as the nurse specialist role in IBD (148). The adjunct of patient initiated, nurse led, telephone consultations has also been well received by patients in this field (149).

Any new intervention, service improvement or future research must be carefully considered to meet patient's needs and ultimately translate into real day to day gains for patients. Along such lines other GI researchers have tried to identify patients follow up needs and model health care delivery accordingly. In Inflammatory Bowel Disease kemp and colleagues (105) found patients wanted to change their traditional follow up with a need for "self-management", "patient initiated consultations" and "virtual care". Cleary every disease has a unique patient population with different needs. As health care professionals or researchers, we must not assume we know what is important to patients or how best to deliver their care. Only by involving them in such processes can their needs be fully addressed. Undoubtedly the use of PPI now extends beyond self-care and healthcare improvement developments. The adjunct of PPI in research processes, particularly research priority setting, is potentially a powerful means of changing the research landscape in favour of the research user.

1.11. Conclusion

In the rapidly changing and uncertain landscape of Barrett's oesophagus and oesophageal adenocarcinoma we must not forget the patient's perspective. Quality of life measures are important assessments of the impact of disease and effectiveness of healthcare. The consequence of Barrett's Oesophagus and its care pathways on quality of life remains unclear. Historical follow up care has perhaps left some patients in the dark with little disease understanding, inaccurate perceptions of cancer and unnecessary psychological burden. A greater understanding of the prevalence of these factors and identifying patients' specific needs will help shape future health care delivery and hopefully improve patient satisfaction.

Table 1.11-1 Summary

What we know	• Barrett's Oesophagus negatively impacts overall QOL scores compared to general population controls • Symptom control is an important factor in maximising QOL • Traditional HRQOL measurement with a generic and disease specific score may miss other important factors. • Patient involvement in self-care, healthcare improvement and research is considered essential. • Clear benefits of PPI in research priority setting have been identified.
What we don't know. Future areas of research.	• What is the true prevalence and impact of poor disease related knowledge, worry of cancer and psychological burden of patients undergoing surveillance? • What is the burden of dysplastic BO, early OAC and their evolving treatment pathways? • What issues are important to patients concerning QOL? • What are patients' needs in terms of their follow up care? • What is the impact of a dedicated Barrett's Oesophagus service? • Is there a role for developing a BO specific patient reported outcome measure? • What are the most effective methods of PPI and how can their impact be accurately assessed? • What are the key future research priorities for patients?

1.12. Aims

- Chapter 2; using qualitative methodologies
    - To identify and explore factors impacting on BO patients' HRQOL.
    - To identify and explore the follow up needs of BO patients
    - To explore patients' perceptions and attitudes to new models of follow up care
- Chapter 3; using quantitative methodologies

    - To identify prevalent factors which may impact on DBO and BO patients HRQOL.
    - To identify any correlations between these factors.
    - To provide comparative cohorts to enhance analysis and broader interpretation of results.
- Chapter 4
    - To identify the key future research priorities important to both patients and clinicians.
    - To facilitate a balanced patient and clinician involvement in the priority setting process.
    - To agree on a final “Top 10 research priorities”
    - To publish the methodology and results in a relevant open access journal.
    - Influence the direction of future research agendas
- Chapter 5
    - To begin to answer a patient centred research uncertainty outlined in “The top 10 research priorities” (chapter 4).

2. Chapter 2 - Barrett's oesophagus: a qualitative study of patient burden, care delivery experience and follow up needs.

2.1. Introduction

In contrast to many other cancers in the western world the incidence of oesophageal adenocarcinoma (OAC), has increased over the last three decades (150-152) with no significant change in survival over the last 10 years (153). In an attempt to address this imbalance, Barrett's Oesophagus (BO) has been identified as a key opportunity to intervene and prevent OAC. With clearer referral guidelines (1) and National public health campaigns (Public Health England "be clear on cancer") (154) the diagnosis of this precursor for OAC will continue to increase (155). Without more accurate and reliable individual risk stratification, the majority of patients with BO undergo long term endoscopic surveillance, which has implications for future healthcare provision and lifelong patient burden. Few studies, predominantly quantitative in design, have demonstrated significant reductions in BO patients' health-related quality of life (HRQOL) scores. However, many of these are now outdated, lack generalisability and have used measurement tools not specific to BO (156). Only in recent years have international guidelines, the British Society of Gastroenterology (BSG) and American College of Gastroenterology, advised consultation and counselling of newly diagnosed patients prior to surveillance enrolment (1,16). Historically, BO patients are likely to have received inconsistent care from poorly informed or even disengaged physicians (144,157). The effects of historic follow up and current care pathways on patients remains unknown.

Traditionally the providers of new healthcare developments have controlled their design and implementation. This archaic "doctor knows best" attitude to healthcare delivery and research has begun to change in the NHS over recent years with a keener focus on patient centred, effective and safe clinical care (123,158-161). This patient involvement is perhaps even more critical in a public funded system where our users are also the main stakeholders. A recent systematic review identified many UK studies citing involvement of healthcare users and the subsequent changes made from their participation in a variety of settings. However reporting of subsequent impact was poor which likely reflects lack of tools available to measure such impact and under reporting (159). Nevertheless, one area where user involvement appears to have its greatest influence is when drawing upon patients' experiences, particularly in chronic disease settings.

Previous engagement with patients to identify and address their follow up needs has dramatically changed the landscape of care in some chronic diseases. Most notably, within Gastroenterology,

have been the developments in Inflammatory Bowel Disease (IBD) Care. In 1991 Probert et al (162) conducted a questionnaire survey regarding disease counselling preferences in 59 patients with IBD. This landmark paper identified a significant number (60%) who required further information regarding their condition. They also found that many patients would be happy with a trained nurse consultation and identified a need for more rapid access to services. Since then the role of the specialist IBD nurse has evolved and been proven to reduce admissions, emergency attendances and outpatient appointments leading to large cost savings (148). These improvements likely reflect enhancements in professional-patient relationships, patient disease specific knowledge, self-care and medication compliance. These endpoints, however, are somewhat harder to measure. More recent research into IBD follow up care found that patients desire more active involvement in their care and are keen to explore more novel follow up alternatives, for example virtual clinics (105).

Although the disease profiles, patient demographic and treatments may differ dramatically between chronic diseases, there are valuable commonalities to draw from these patient involvement strategies and service improvements. In particular these include the processes used to involve patients and seek alternative or enhanced ways to educate, follow up and communicate with patients.

2.1.1. Aims

- To identify and explore factors impacting on BO patients' HRQOL.
- To identify and explore the follow up needs of BO patients
- To explore patients' perceptions and attitudes to new models of follow up care

2.2. Methods

This exploratory qualitative research, forms part of a concurrent mixed methods study, using both qualitative and quantitative data collection tools, to explore the impact of BO on patients HRQOL (163), their experiences of follow up care and attitudes towards service developments in line with preliminary research needed when developing complex interventions (164). This qualitative approach, attempts to understand social phenomena in natural circumstances, with an emphasis on exploring meanings and views of participants (165). The study design incorporates the Consolidated Criteria for Reporting Qualitative studies (COREQ) guidelines (166) (supplementary appendix 8.1.1)

2.2.1. Ethical Considerations

Prior ethical approval for this study was obtained from the Health Research Authority Yorkshire and Humber ethics committee (REC reference number 16/YH/0035).

2.2.2. Participants and Setting

Individuals with BO, enrolled in surveillance at a single General NHS Hospital, were targeted because they were readily accessible within the constraints of the study team geography. Participants were purposively (167) recruited with the aim of achieving maximum variation in terms of disease duration, age and gender even though this is a male predominant disease. Recruitment continued until a point where data saturation was reached i.e. where no new themes emerged from additional interviewees (168), however the authors recognise this remains a contested concept (169,170), based on the researcher's subjectivity of what they are hearing (171). Participants were recruited face-to-face at their surveillance endoscopy, via telephone or postal invite. There was no prior contact between researchers and participants before recruitment.

2.2.3. Data Collection

Semi-structured, in-depth one to one interviews were undertaken by JB (average time of 40 minutes, range 21-76 minutes). The status of the interviewer (postgraduate research doctor) was made aware to all participants. An interview topic guide was developed from a prior literature review (156) and expert opinion (supplementary appendix 8.1.2). Interviews focused on the impact of surveillance, physical and psychological symptoms, experiences of follow-up care, follow-up needs and new models of follow-up care. New models of care included a dedicated BO service and patient-initiated consultation by means of telephone or virtual clinic. All Interviews were conducted in a private seminar room to provide a non-clinical atmosphere. Interviews were audio recorded, transcribed verbatim and anonymised prior to analysis. Participant's demographics and disease specific information were also collected from their medical notes and endoscopy reports. Field notes were taken at the time of each interview. These written recordings captured important verbal and non-verbal information which can be overlooked once the content is transcribed. This is an important step to keep the context of the interview.

2.2.4. Data analysis:

A thematic analysis was conducted on all data, using a framework approach (172) supported by NVivo Pro 11. The key steps are outlined in figure 2.2.4-1. This widely used approach (173) allows

rigorous analysis without losing transparency or site of the initial raw data. Initial emerging themes were identified from the first 4 interviews. These themes, alongside topics raised from the interview guide, formed the conceptual framework (table 2.2.4-1) (supplementary appendix 8.1.3). This framework was then applied manually to the raw data in a process called indexing. Field notes were linked to the content with clear associations between themes recorded for later use in descriptive analysis. The fully indexed raw data was then displayed in thematic charts allowing greater focus and distillation of the detail in each sub-theme (supplementary appendix 8.1.4) (an example of a fully indexed thematic chart is also available to view on the supplementary USB appendix 9.1.1). Each column of the thematic chart was then subjected to descriptive analysis and further interpretation of the data to recognise patterns and explanations, the evidence of which is displayed in the framework analysis concept map (supplementary USB appendix 9.1.2).

Figure 2.2.4-1 Framework Analysis

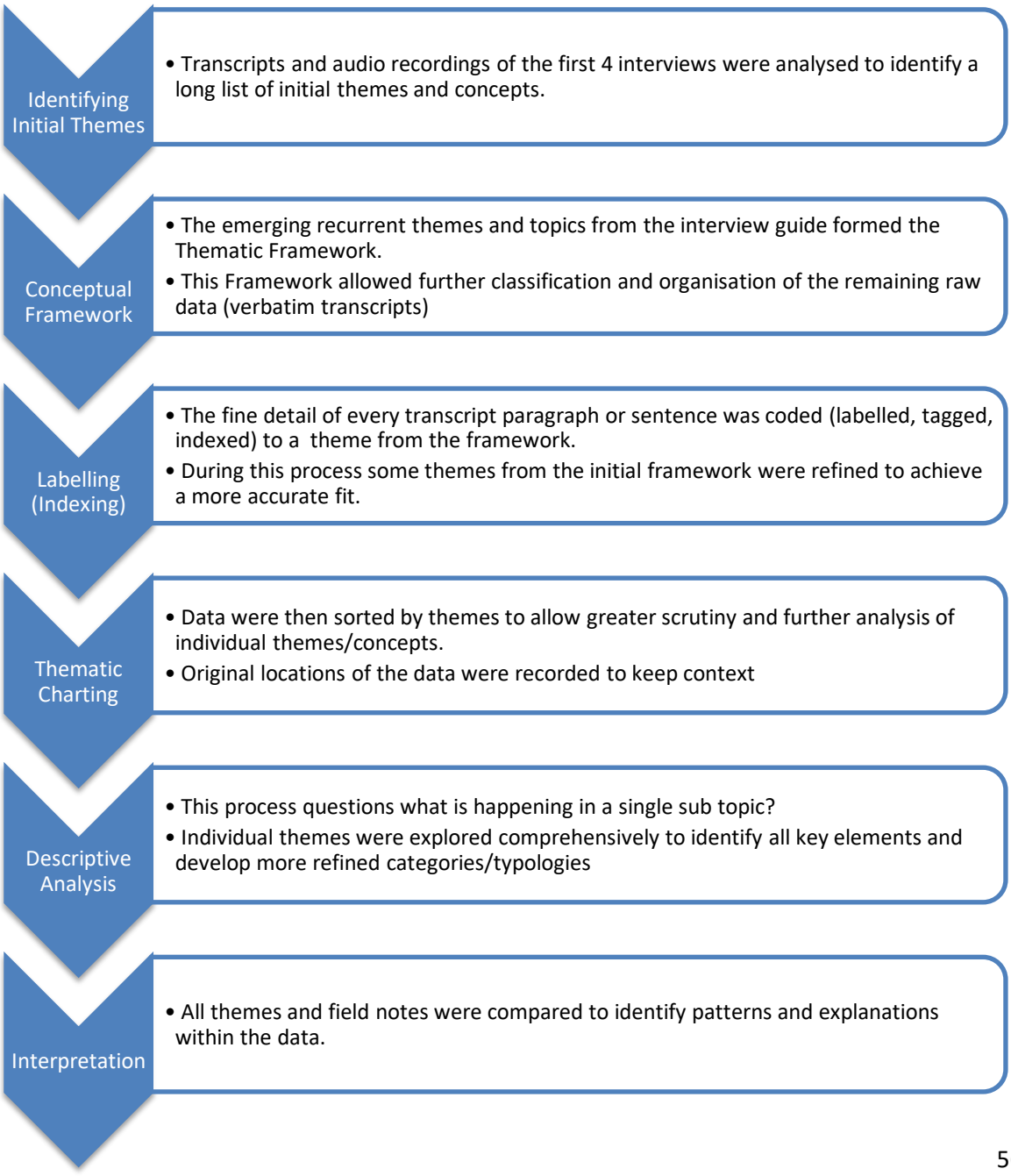


Table 2.2.4-1 Conceptual Framework

Initial Main Themes	Initial Categories	Contributing participants (n/20)	Verbatim quotes
1. Controlling Symptoms	1.1 Impact of Medication on symptoms	18	40
	1.2 Changes to Lifestyle	20	68
	1.3 Managing symptom flare ups	19	40
	1.4 Attitudes/Concerns regarding medication	19	31
2. Disease Impact	2.1 Physical symptom impact	18	59
	2.2 Associated worries/anxieties	20	106
	2.3 Surveillance endoscopy impact	19	65
3. Disease Specific Knowledge	3.1 Disease specific knowledge and health beliefs	20	96
	3.2 Knowledge gaps	16	68
	3.4 Information sources	19	78
4. Follow up Experiences	4.1 Experiences with secondary care at time of diagnosis.	20	71
	4.2 Experiences of surveillance endoscopy	19	81
	4.3 Experiences with primary care (GP)	19	50
	4.4 Value of surveillance endoscopy to them	19	62
5. Follow up Needs	5.1 Unmet needs	18	62
	5.2 Value of seeing an expert	12	31
	5.3 Other ideas offered	14	37
6. Attitudes to new models of follow up care	6.1 Dedicated Barrett's oesophagus service	20	77
	6.2 Patient initiated telephone consultation	20	78
	6.3 Patient initiated online consultation ("virtual clinic")	18	39

2.2.5. Rigour

The following steps were taken to ensure rigour. Firstly, none of the participants had prior clinical contact with the researchers. The topic guide was reviewed by all researchers to ensure appropriateness of the content. Field notes were taken during each interview to ensure grounding of the content during analysis. Finally, two initial verbatim transcripts were analysed by two different researchers (JB and MH, a qualitative research specialist with a clinical background in

nursing to confirm the data was within the remit of the study and the initial emerging themes identified were consistent and fit the data captured. Preliminary findings were discussed between JB, MH and YA who agreed upon the relevance of the data and credibility of the analysis. Consensus on themes was reached through discussion.

2.3. Results

Data saturation, the point where no new information emerged from the data (174) occurred after 20 participant interviews, the demographics of which are displayed in table 2.3-1. In total this process generated three overarching themes and 10 subthemes (figure 2.3-1). Considering the aims of the study the results will be discussed under the three main themes 1) Burden of disease, 2) Follow up experiences and 3) Follow up needs. Information describing each theme is given and supplemented with original verbatim quotes.

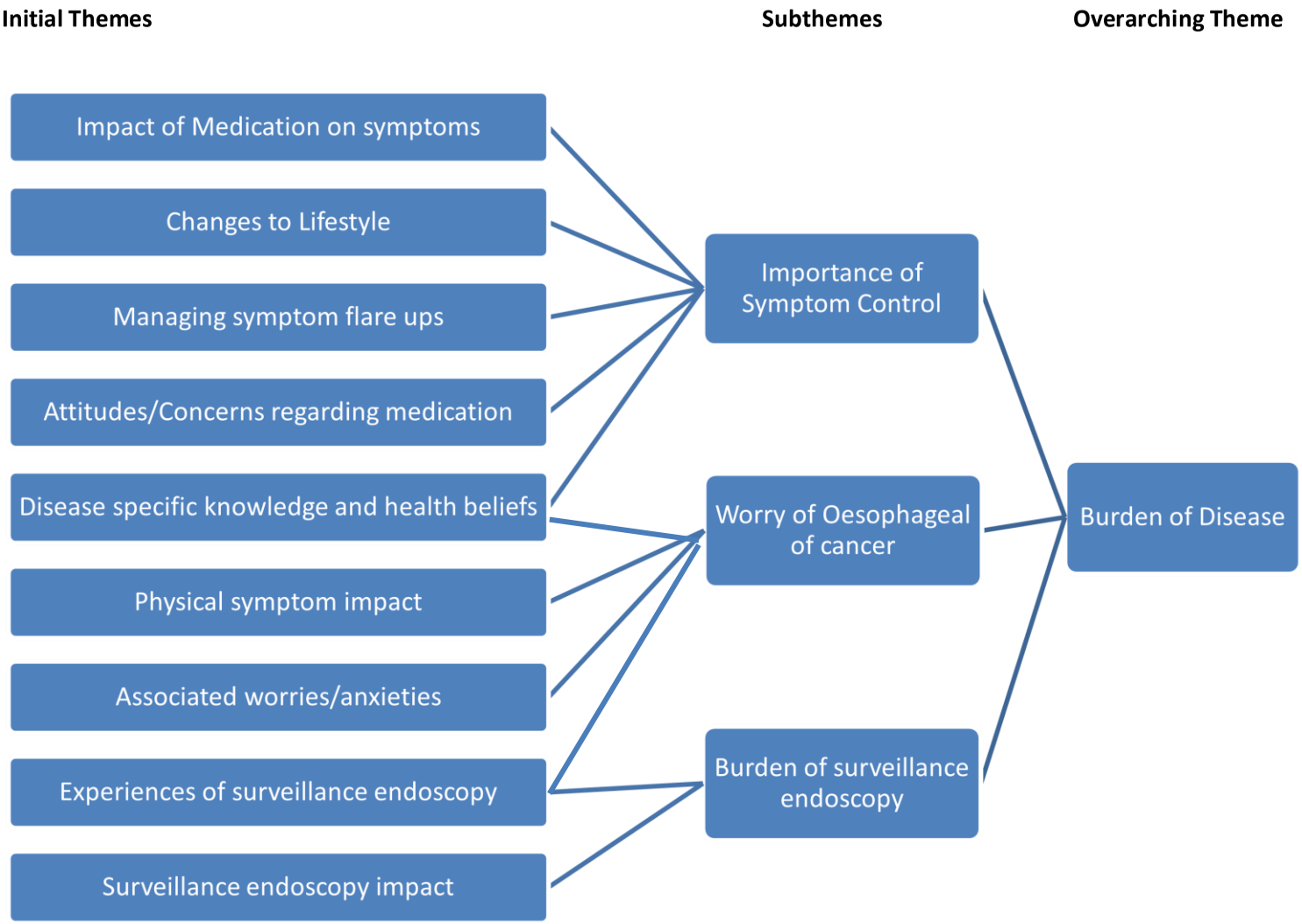
Table 2.3-1 Participant Demographics and Characteristics

Participant	Age	Gender	Disease Duration	Prague Classification	Co-Morbidities
A	56	M	4yr 7 months	C2M4	Hypertension
B	71	F	2yr	C2M4	Asthma, coeliac disease, osteoporosis
C	69	M	10yrs	C10M10	Hyperlipidaemia
D	42	M	4yrs	C0M5	None
E	65	M	1yr 8 months	C2M3	High cholesterol, hypertension
F	66	M	8yr	C2M3	Pulmonary fibrosis
G	58	M	7yr 1 month	C2M4	Hypertension, musculoskeletal pain
H	62	M	2yr 2 months	C4M6	None
I	77	M	1yr 5 months	C2M4	Hypertension
J	46	M	4yr 6 months	C0M2	None
K	61	F	8yr 2 months	C1M2	Previous thyroid cancer, hypertension
L	70	M	2yr 4 months	C6M7	Ischaemic heart disease, abdominal aortic aneurysm.
M	50	M	4yr	C2M2	None
N	61	M	4yr	C9M10	None
O	76	M	6yr 6 months	C6M6	None
P	66	M	1yr 9 months	C2M4	None
Q	76	F	13yr 3 months	C8M8	Rheumatoid arthritis, hypertension
R	58	F	11yr 2months	C8M8	Depression, osteoarthritis, previous joint replacement, previous gastric bypass.
S	63	F	3yr	C4M5	Osteoarthritis
T	65	M	15yr 10 months	C0M3	Hypertension

M = Male, F = Female. CnMn = Circumferential and Maximum BO measurement.

Age (Median= 63 years, Range= 42-77 years). Disease Duration (Median= 5.8 years, Range= 1-15 years), Prague Classification (Median=C3.6M5, Range= C0-10, M2-10),

Figure 2.3-1 Developing an overarching theme



2.3.1. Burden of Disease

Importance of Symptom Control

All patients reported effective long-term symptom control due to the positive impact of medication and or lifestyle interventions with little impact on their activities of daily living. Achieving consistent symptom control remains highly important to patients as most recall a significant impact on their quality of life pre-treatment. Some also report disruptive symptom flare ups which interfere acutely with their quality of life for example social occasions. These can be unpredictable and challenging to manage. The strategies adopted, confidence and ability of patients to self-manage flare ups varies widely. Active symptoms also appear to cause anxieties regarding disease progression and worry of oesophageal cancer with some participants seeking medical attention and sooner endoscopies via their GP.

"It was a new lease of life for me because I wasn't having the horrible symptoms because of the tablets. I was very pleased with the tablets and I still am." (A, 56yr, male)

"I can take my medication and not change my diet but every so often you get a really bad, severe, like burning in my throat and back pain and it feels like someone's put an axe in your back. I might be in a circle with a few friends and suddenly you have to disappear, you have to make apologies for leaving because of the pain". (D, 42yr, male)

Worry and Anxiety of Oesophageal Cancer

Some participants are able to put thoughts regarding cancer "to the back of their mind" or approach cancer risk pragmatically with a "what will be will be" attitude. One participant's perspective of BO cancer risk changed dramatically to one of little significance after receiving a diagnosis of a more life-threatening disease (F, 66yr, male). However, many patients do report worry or anxiety regarding developing oesophageal cancer. This appears to be most strongly associated with times of poor symptom control or in the weeks preceding their surveillance endoscopy. There was no correlation with degrees of cancer worry and participants length of Barrett's oesophagus (Prague classification), a recognised individual risk factor. Factors which seem to enhance or precipitate worry include an anxious predisposition, past or personal experiences of cancer, having dependents, inaccurate or poor disease specific knowledge and waiting times on the day of their surveillance test or indeed in the weeks afterwards for biopsy results.

Participants with more adequate disease specific knowledge and an internal locus of control seemed to report less cancer related worry. Immediate verbal communication of surveillance test

results also helped prevent anxiety over biopsy results in the weeks following endoscopy. Enrolment into surveillance was also a big factor in helping reduce worry of cancer. Considering the lack of RCT evidence for the efficacy of surveillance nearly all participants, perhaps wrongly, overvalue its protective effects. When asked about their response to an overdue surveillance test (i.e. exceeding the planned or expected surveillance interval) nearly all participants would actively chase this up and would strongly question health professional advice to discontinue surveillance.

"It's just that a lot of close people have died recently of cancer, so it's gets you thinking doesn't it. I've got a young family at home, so yeah, it's a massive thing. Every time I get symptoms I start worrying. And obviously you don't want them symptoms, you just want to live a nice healthy life." (D, 42yr, male)

"I think I'm coming here every two years to get it checked and if there is any problem it'll be found straightaway, and that's always at the back of my mind, and that stops me from worrying about it. I know I've got this problem but it's controllable. And I don't feel of any risk of anything. I don't know if that is wrong but that's how I feel." (C, 69yr, male)

Burden of Surveillance Endoscopy

Anxiety and worry surrounding surveillance endoscopy is not solely related to thoughts of disease progression but to the physical implications of the test. Many patients find the test physically burdensome, intrusive with a sense of it being out of their control. The main physical distresses reported were during the test rather than afterwards, these included difficulties swallowing the camera, uncomfortable retching, choking and coughing. In such cases anxieties can build from the moment they receive the appointment and climax on the day of the procedure, this is exacerbated further by the waiting time in endoscopy. Effective communication from healthcare professionals in the procedure room appears vitally important in counteracting this and helping them cope.

""It's terrible. It affects me for weeks before and not just on that day. Just the thought of what's going to happen. And it was an awful, awful sensation. And then it went on and on. They weren't talking to me, which is very, very important. You can't reply to them but nevertheless you want something, you know, "everything's fine, we're halfway through now, it won't be long now", something like that would make a lot of a difference."" (O, 76yr, male)

2.3.2. Follow up Experiences

Inadequate follow up at diagnosis

Participants experiences of secondary care follow up at the time of their diagnosis was inconsistent and in the majority of cases inadequate for their needs. The majority of patients received a brief interaction post endoscopy either from the endoscopist or nurse at discharge. In some instances, Barrett's oesophagus was not discussed at all. In these cases, participants received notification via a copy of their endoscopy report or subsequent letter. In one case the participant was unaware of the diagnosis until they were asked to attend for their next surveillance endoscopy. Such inconsistencies and inadequacies could be predicted considering the BSG have only recommended outpatient clinic follow up since their latest guideline publication in October 2013. However, those who did receive clinic follow up also reported mixed experiences with some feeling the clinic was too time pressured, with a lack of emphasis on Barrett's and left with unanswered questions.

"When I came in and I sat down in the waiting room before I went in for my camera, the nurse told me I've got Barrett's. So, it must have been found at an earlier date and I was never informed that I'd got it." (E, 65yr, male)

"I know time is of the essence sometimes, you know…It was sort of coming off the production line type of thing. I didn't think it was informative enough. I mean, when somebody hits you with like two different things as well, you know, Barrett's and a hiatus hernia, it said it was 2 to 3 cm. Now, that seems big to me and I didn't know what to do about it really." (P, 66yr, male)

Primary Care Experiences

Engagement with primary care was minimal at the time of diagnosis in most cases. Participants would, and in some cases, have relied upon their GP as the first port of call during an unmanageable flare up of symptoms. Those with greater continuity of care and longer-term relationships with their GP appeared to have more satisfaction and trust in their GP's abilities to deal with their BO. However, many reported difficulties getting appointments quickly and poor continuity of care with surgeries increasingly using temporary staff. Some participants felt their GP was dismissive or lacked knowledge regarding BO with a heavier focus on medication changes rather than lifestyle interventions.

"Your GP knows you, you know them. They know what issues you've been facing over the years. They know how it's progressed or how it's being controlled. Whereas the locum (temporary staff) will go through the textbook you know…. try this, this, and this. I did try that quite a while ago if

you look at the notes, go back and back and back, and they haven't got time to be doing that." (H, 62yr, male)

Inadequate Disease Specific Information

Inadequacies of follow up care provisions appear to have led to poor disease specific knowledge in most cases with no clear association to any of the demographics collected. For example, some participants hold inaccurate views of exactly what BO is, while others over or underestimate their cancer risk. Misleading or inadequate knowledge, in some cases, appears to have detrimental effects such as enhancing cancer worry or reduce their ability to self-manage symptom flares. The majority of participants have acquired information verbally on an ad hoc basis from their GP or healthcare professionals at the time of their endoscopy with some cases receiving written information in the form of a leaflet or copy of their endoscopy report. Any written information appears welcomed by participants but this often led to further questions or, in the case of the endoscopy report, was difficult to interpret due to the use of medical jargon.

Nearly all have sought further information and are predominantly self-educated via the internet, newspaper articles, books or radio shows for example. The internet was by far the most common resource used, however, participants expressed concerns and fears over obtaining inaccurate worrisome information with no clear guidance on where to find trusted sources online. This finding was present in both younger and older participants. Some patients expressed concerns that improved disease specific knowledge may heighten anxieties regarding oesophageal cancer and were least likely to seek additional information preferring to adopt an "ignorance is bliss" approach. In comparison, over estimators of cancer risk were linked to heightened anxieties and worries of cancer, whereas those who correctly viewed their risk as low, generally, appeared to have less worry.

"This leaflet, there's just broad headings. It was given to me the last time I was discharged (from endoscopy department). It's not exactly a big document. It's good, I know now what Barrett's is. But so what? If something leaves the question of 'so what?', it hasn't done enough." (L, 70yr, male)

"I've had very little information from health professionals. I've had to educate myself with Dr. Google which is not brilliant….no dietary or lifestyle advice whatsoever. Again, it was down to me to search that out." (F, 66yr, male)

2.3.3. Follow up Needs

Greater Disease Specific Knowledge

The major unmet need identified was disease specific knowledge, particularly at the time of diagnosis. This was apparent in those with short and long disease duration. Some patients still harbour significant unanswered questions years after diagnosis. Nearly all patients ideally would have preferred a face to face consultation after diagnosis to allow questions and, if necessary, attendance of their next of kin. Few participants would have preferred the delivery of this information via consultation immediately after their initial diagnostic procedure. Practically this approach is less feasible when one considers sedated patients, the processing of biopsies and time pressures in an endoscopy department. Participants were able to identify current knowledge gaps and key uncertainties they would want addressing at the time of diagnosis (table 2.3.3-1). Although those who received copies of their endoscopy report didn't find them very informative, they did find the associated diagrams and pictures of their oesophagus both useful and interesting.

"I would have liked to know what caused it. What are the chances of it, you know, becoming cancerous? What treatment is available? I would have just liked to know more about it really. It's a bit scary." (K, 61yr, female)

Table 2.3.3-1 Disease Specific Knowledge; Patient Uncertainties

Sub-topic	Patient uncertainties
1. Barrett's oesophagus	What is Barrett's oesophagus?
	What Causes Barrett's oesophagus?
2. Oesophageal cancer risk	What are the stages of the disease?
	What is my risk of oesophageal cancer?
3. Role of surveillance	What are you looking for during surveillance?
	Are there other options to surveillance?
4. Medical Treatment	Why do I need to take PPI's long term?
	Are PPI's safe to take long term?
	Can Barrett's oesophagus be reversed?
	If things change what treatment is there?
5. Lifestyle	What can I do to improve my symptoms?
	What can I do to reduce my risk of cancer?
6. Managing acute symptoms	How can I manage symptom flare ups?
	When should I seek medical help?

Value of Seeing a Specialist

When asked about improving delivery of care and reflecting on their past experiences it was clear that patients highly value face to face interaction with a specialist. This probably reflects past inadequacies of secondary care follow up and the concerns some have over their GPs knowledge, ability and attitude towards Barrett's oesophagus. Potential benefits identified included greater expertise, experience, continuity of care and reassurance. Some patients also report to be more likely to follow verbal advice from a specialist than written information. Those with additional chronic health conditions, such as heart disease (T, 65yr, male), reflected warmly on other specialist input and appeared to seek the same in their BO care.

"I'd like someone with knowledge to be able to talk me through it, the pros and cons, the risks, and what the standards or whatever they would be, to be applied but with knowledge, not just to be given the briefest bit of information but given options as well." (F, 66yr, male)

"I don't think my doctor (referring to GP) would be able to give the right level of reassurance because they're not going to have that day-to-day practise of working in that area." (J, 46yr, male)

"Whoever's on duty at the time, obviously know about Barrett's, but obviously don't have a big interest in it. Like I said when you're going in (e.g. to an endoscopy appointment), everybody's going for something different aren't they. When I was going in they said…. ""What are you coming in for?"". If it was a specialist, they would know what I was coming in for, wouldn't they." (P, 66yr, male)

"If you're speaking to someone specialising in it, that's their main interest, so you've got their attention. Plus, you know, there's always someone there who understands the condition and if you have got any concerns you feel like they know what you're talking about." (S, 63yr, male)

Improved Communication, Organisation and Structure during secondary care follow up

Endoscopy staff (Endoscopist, endoscopy nurse and healthcare worker) communication appears vital in maximising the patients experience during surveillance endoscopy. In particular reassurance during the procedure and clear verbalisation of encouraging endoscopy findings afterwards. Participants who had experienced endoscopy at both sites of this hospital favoured the diagnostic outpatient endoscopy suite over the acute hospital site. This was predominantly due to staff attitude, atmosphere, accessibility and waiting times in the department. Participants also sought

greater continuity and fluency of care during their follow up. In particular some faced difficulties when making endoscopy appointments, including chasing overdue tests.

"I think the mannerism with the staff helps an awful lot. When you walk into an atmosphere where everybody is pleasant type of thing that helps settle you down. If the people who are doing it are anxious that would make you more anxious. And it's always nice to know that the people around you know exactly what they're doing." (G, 58yr, male)

Perceptions of new models of follow up care

Dedicated Barrett's oesophagus clinic and Endoscopy

Patients were asked about their views on the implementation of a dedicated Barrett's service. This service, run by a healthcare professional (gastroenterologist or nurse specialist) with a specialist interest, would encompass both surveillance endoscopy and an outpatient clinic. All participants responded positively to this concept. In particular they liked the face to face contact with a specialist and thought it could potentially solve the continuity of care issues currently faced. When asked specifically about the provider of this care the majority of patients would be happy to see either a specialist doctor or nurse. Very few, but typically older male participants, had some reservations regarding this such as appropriate training or supervision of the nurse specialist. Individuals with other chronic diseases, such as rheumatoid arthritis, related to positive experiences with other nurse specialists (for example participant Q, 76yr female). Some patients eluded to other potential enhanced outcomes such as improved disease specific knowledge and greater reassurance. Others were surprised that surveillance endoscopies were conducted by so many different people and suggested the test may be conducted more thoroughly if done by fewer, more experienced individuals.

(re dedicated clinic) "" I think that's what is really needed to be quite honest, from my point of view. There's just not enough information out there, concrete information. I think it gives more confidence to the patient, rather than just saying "look at this information leaflet and follow that to the best you can."" (P, 66yr, male)

(re dedicated list) "That would be good because, obviously, the man with the camera is just doing one after another probably different procedures, like I said he's no specialist in Barrett's. I mean when you're going in, they had to ask me what I am coming in for. I think it will be a lot better. Obviously, if they're more trained in Barrett's they know what they're looking for." (R, 58yr, female)

(re nurse care provider) "that would be good as long as they specialise in that particular area. Because for example when you ask your GP, sometimes he won't want to commit or wrongly advice you, and sometimes he'll probably just look on Google. (D, 42yr, male)

(re nurse/doctor care provider) "I don't think it makes any difference as long as they are keyed up on the subject, why should it?" (G, 58yr, male)

Patient Initiated consultation.

All participants were asked about their ideas, concerns and potential usage of a patient-initiated consultation service. They were asked to consider two different approaches, firstly a telephone direct access line where patients can leave a message and be contacted back by a member of the dedicated Barrett's service. Secondly, an online "virtual clinic" where patients can upload their concerns or symptoms and be contacted back in the same manner. All participants liked the overall concept of a patient-initiated consultation, especially the direct and quicker access to specialist services which bypass and therefore free up GP time. Patients liked the idea of a reassuring "safety net" and drew comparison to other specialities, such as ENT and rheumatology, where they had benefited from similar systems. Nearly all participants preferred the telephone consultation over an online clinic. The main reason for this was the impersonal nature of using a computer and concerns over IT literacy and computer access in older generations. Some were also concerned, in general, about inappropriate use and cost of the service, suggesting there needed to be clearly defined triggers to guide self-referral.

(re online clinic) "Well, it goes back to banking doctor, my husband and I are old school we like to speak to somebody at the bank over the counter because we're not into the internet. It's nice to speak to somebody." (Q, 76yr, female)

(re online clinic) "I mean people's IT skills are improving all the time, and mine are okay, but I still don't think it's the most appropriate way to deal with things because it's impersonal." (H, 62yr, male)

2.4. Discussion

This study aimed to explore BO from the patients' viewpoint, in particular, the impact on health-related quality of life, experiences and effectiveness of follow up care and opinion on new follow

up systems. To our knowledge, this represents the most in-depth account of BO patients' perspective of disease impact in a UK NHS setting.

The most striking finding relates to patients experiences of follow up care. Historic and current follow up for BO appears inconsistent and often inadequate to meet patients' needs and expectations. This has led to poorly informed patients with limited or inaccurate disease specific knowledge. Some potential impacts, identified in this study, include reduced confidence and ability to self-manage symptoms and heightened cancer specific worry. Very few studies exist which assess levels of patient education in BO. Concerningly, in 2008, Murphy and colleagues reported less than 50% of patients with concurrent OAC and BO diagnoses were aware of their BO diagnosis despite an average of more than 7 previous endoscopies (175). Improved patient knowledge in inflammatory bowel disease appears to have positive and detrimental effects with greater knowledge associated with adaptive coping strategies but also higher anxiety levels (176,177). This reflects those who report an "ignorance is bliss" attitude too improving disease specific knowledge in this study. Even participants with longer-term diagnoses voiced unmet needs and questions regarding their condition. This finding questions the current BSG guidance which only recommends new patients attend an outpatient clinic (1). The role of a Barrett's clinic may be much broader than this, by giving all patients the option of attending clinic after their surveillance endoscopy would capture patients seeking more information and guidance about their condition. In some cases, it may also provide a platform for addressing poor symptom control or an opportunity to discuss the appropriateness of discontinuing surveillance. The latter may be vital when one considers the number of patients who may have been enrolled in surveillance inappropriately (64,178) or indeed in a time when diagnostic criteria were less clear. Discussions regarding cessation of surveillance are unlikely to be adequate or satisfactory to patients at the time of endoscopy as this study has shown patients hold strong beliefs regarding its protective efficacy. A clinic appointment specifically to explain the reasons for cessation of surveillance, for example in medically unfit patients where the risks out weight the benefits, may help patients understand and accept the physicians' recommendation with less anxiety.

The findings suggest that BO patients have three key potential impacts to their HRQOL: symptom control, worry of oesophageal cancer and burden of surveillance endoscopy. Overall patients generally report good long-term symptom control with little impact on their daily lives. This finding may reflect previous quantitative work which shows reflux symptoms in BO cohorts are commonly better than those with a diagnosis of gastroesophageal reflux disease (5,53,54). However, consistent control remains imperative as a significant minority suffer from symptom flare ups which interfere with activities of daily living and in some cases, trigger worries of disease progression, specifically oesophageal cancer. This intermittent effect may not be captured during quantitative

HRQOL questionnaire assessments when one considers the lack of a validated BO patient reported outcome measure and varying questionnaire recall periods.

The other chief trigger of cancer worry is an approaching surveillance endoscopy. This acute worry may be harder to modify and is a well-documented impact of cancer prevention activities (60). Pre-test worry and anxiety was also strongly associated with the physical implications of the test with many patients reporting the endoscopy as physically burdensome. Although past research suggests patients undertaking the test for symptoms rather than BO surveillance find the test even worse, implying patients burden may reduce with repeated exposure (95). Enhancing patients' experience of surveillance endoscopy appears multifactorial but should focus strongly on healthcare professional communication during and after the procedure. These findings are supported by previous quantitative work. Kruijshaar and colleagues reported lower anxiety scores after endoscopy than beforehand in BO patients (66,95). This probably reflects reprieve from reassuring results and the relief of completing a physically taxing test. However, anxiety levels in this study remained raised one month after endoscopy when compared to those who underwent endoscopy for non-specific upper gastrointestinal symptoms. This may reflect unnecessary anxiety over biopsy results or indeed a more chronic issue.

There is a clear need for change in BO follow up care. In particular patients require greater information at the time of their diagnosis. This finding is comparable to research in other chronic diseases, in particular IBD where there has been development of knowledge measurement tools (179,180) and research highlighting the positive effects of a patient education (181). Patients clearly value the role of a face to face consultation with a knowledgeable health care professional. This two-way discussion should cover both the professional and patient agendas (table 2.3.3-1) with the adjunct of visual aids, ideally diagrams or pictures from their own endoscopy. Patients should also be given the option of additional written information or website details. Patients strongly believed this should be an aide to discussion not a replacement of it. It was also clear that patients' experiences at endoscopy varied widely with a lack of continuity of care. In order to improve patients' experiences healthcare professionals should focus on clear reassuring communication within the endoscopy room including verbalisation of encouraging results to minimise post endoscopic worry. This finding is supported by previous qualitative work which identified factors that may influence patients' adherence to BO surveillance. The doctor patient relationship was deemed vital in particular, communication prior to, interaction during and levels of trust after endoscopy (147). Other, logistical, areas of consideration for endoscopy departments should include waiting times on the day of procedure, ease of making appointments and the potential influence of a more calming "non-acute" atmosphere for patients. It may be favourable for surveillance patients to attend an evening or weekend list when departments are less busy and waiting times are less likely to be lengthened by the demands of acute care. In hospital trusts with

two separate endoscopy sites (elective and acute), the environment for surveillance endoscopy in the elective site is more likely to be ideal.

In order to develop BO follow up care this study not only assembled patients past experiences, but sought their views on how to enhance care including their opinions on suggested new models of follow up. Alternative approaches to care were met positively, in particular a dedicated service which would provide a lynch pin between clinic and endoscopy at a secondary care level. This may address their main needs surrounding specialist input, improved continuity of care, organisation and structure. In other studies, patient preferences towards follow up care provider (secondary vs primary care) after cancer survival is mixed and appears influenced by multiple patient and provider factors (182) which may vary significantly across diseases and healthcare systems. This study showed a strong patient preference towards improving secondary rather than primary care follow up. This likely reflects a lack of GP emphasis on Barrett's oesophagus coupled with poor continuity of care experienced. Patients are also aware this is largely an endoscopically monitored disease and therefore may lean towards a secondary care point of contact to facilitate access to endoscopy if necessary. As the BO research landscape moves forward guidelines will change and newer surveillance endoscopy techniques are likely to be adopted. A dedicated service would also allow easier transition ensuring up to date, consistent and standardised care. In fact, some of the concerns regarding enhanced endoscopic surveillance techniques relate to their reproduction outside tertiary settings and additional training required for multiple endoscopists (183).

Participants also liked the concept of a "safety net" in the form of a patient-initiated consultation service. This probably reflects the potential impact of uncontrollable symptom flares, length of time in-between endoscopies and doubts over primary care ability to deal with their concerns in a timely manner. Patients had a strong preference to a telephone-based system rather than an "impersonal" virtual clinic which may exclude patients who lack computer access or IT literacy. This is in contrast to other chronic diseases, for example IBD, where E-Health technologies have been both acceptable and beneficial (106,184,185). This likely reflects the average age of 65 years in UK BO surveillance cohorts (157). It is unclear how frequent patients will engage with this service and its wider benefits are hard to measure. Such benefits may include; freeing up GP time, addressing worrisome symptoms, improving access to or preventing over use of endoscopy. Nevertheless, this should be piloted cautiously to assess appropriateness of use and patient satisfaction.

Based on the findings of this study we propose the implementation of a dedicated service encompassing a Barrett's clinic, surveillance endoscopy list and direct access line. This complex care intervention could be delivered by a nurse endoscopist alongside a consultant gastroenterologist, both with a specialist interest in BO. Further research will be needed to assess the practicalities and efficacy of this intervention. Ideally this should be prospective, randomised and compared to

current standard practice. Considering its complexity there must be multiple outcome measures or a dedicated BO PROM which captures all aspects of the patients' perspective (symptom control, worry of cancer, disease specific knowledge and burden of endoscopy). Once psychometrically validated, such a score would make BO HRQOL assessment less cumbersome, more sensitive and consistent, with greater allowance for cross study comparisons in future clinical trials. Further consideration would be needed regarding the potential clinical outcome measures, for example dysplasia diagnosis rates, which are out of the remit of this paper.

2.4.1. Strengths and limitations

The study utilised a number of steps to ensure rigour in its design, however there are some limitations. Firstly, participants in this study were recruited through a single district general hospital population. Therefore, one must be cautious when generalising these findings as all BO care may not be delivered in the same manner, especially those relating to organisation and structure of care which may differ significantly elsewhere. Secondly, the study did not take a longitudinal approach to identifying BO impact over the life course. However, participants were recruited until the researchers were happy that thematic saturation was achieved with good variation of age, disease duration and gender. Variation in socio-economic status and health literacy was not formally sought and this may be an area for future research to clarify. Thirdly, the data captured may have been influenced by the status of the interviewer (186). Fourthly, only 2 interviews were coded by 2 separate researchers which may introduce bias, however there was strong correlation of findings and all authors reviewed and agreed upon the final themes and credibility of the analysis. Finally, all participants were "white British" and English speaking, so one must be cautious when translating these findings to more diverse ethnic populations. A greater number of male than female participants could be viewed as a limitation, however this is a disease predominantly affecting men with a male/female sex ratio of 1.96/1 in a meta-analysis (187).

2.5. Conclusions

This qualitative research provides an in-depth account of the patient perspective of BO in an NHS setting. Key potential impacts on patients include: symptom control, worry of oesophageal cancer and burden of surveillance endoscopy. These factors must be considered when implementing future care pathways, designing clinical trials or developing a BO specific patient reported outcome measure. Follow up care, at this NHS hospital, was found to be inconsistent and often inadequate to meet patients' needs. Patients require greater disease specific information, enhanced

communication, organisation and structure of care. To improve patient experiences, we recommend the design, implementation and prospective assessment of a complex care intervention, which encompasses dedicated BO surveillance, outpatient clinic and telephone direct access line.

3. Chapter 3 – A comparative quantitative survey of patient experience in Barrett's oesophagus

3.1. Introduction

The incidence of oesophageal adenocarcinoma (OAC) and its precursors, gastroesophageal reflux disease (GORD) and Barrett's oesophagus (BO), are increasing (151,188). BO is a well-established, relatively low risk (6), precancerous diagnosis which requires long term endoscopic surveillance as per multinational guidelines (1) (16). Without early detection, OAC is often devastating in terms of prognosis (3). However, the majority of patients with BO will never develop OAC but must live with the burden of a precancerous label. Recent advances in endoscopic therapy (ET) for those who develop dysplasia or early OAC are extremely reassuring with durable outcomes (100). These patients still face multiple endoscopic procedures, long term surveillance and risk of disease recurrence (1,2,16,101). Little is known about how these diagnoses and care pathways affect patients Health related quality of life (HRQOL).

HRQOL "reflects physical, social and emotional attitudes and behaviours of an individual as they relate to their prior and current health state" (29). HRQOL is therefore a key outcome measure of healthcare delivery and treatment efficacy. Despite this, HRQOL assessment in many studies is poorly done or tokenistic (130). To date there is no validated BO specific patient reported outcome measure (PROM). Past quantitative research has therefore used numerous instruments to capture the impacts of this precancerous disease. Significant reductions in generic (e.g. SF-36 form) and disease specific (GORD or gastrointestinal) HRQOL scores have been reported. Prior literature review (156) and qualitative research (189) has identified key areas of interest when measuring HRQOL in BO patients. These include; GORD symptom control, psychological effects (e.g. anxiety and depression), worry of oesophageal cancer and burden of repeated surveillance endoscopies. The few historical studies concerning BO HRQOL are outdated and cannot be translated to current care pathways. Other limitations include underpowered samples, use of a single measurement tool or a lack of appreciation for confounding factors. Even less research has been conducted regarding the impact of dysplastic Barrett's oesophagus (DBO). To our knowledge only 3 prior studies have attempted to assess the patient impact of DBO or BO with early OAC treated endoscopically (radiofrequency ablation and endomucosal resection). One of which was conducted during the AIM dysplasia trial and used an unvalidated measure (85). The other two studies were conducted in single centres (Netherlands and US) with less than 50 participants per group (190) (103). Therefore, the true prevalence of HRQOL detriments remains largely unknown, particularly in a UK NHS setting. Quantitative assessment of such factors will provide a valuable insight into the problem's patients

may face, efficacy of current care and highlight areas future health care delivery can focus resources upon.

3.1.1. Aims

1) To identify prevalent factors which may impact on DBO and BO patients HRQOL.
2) To identify any correlations between these factors.
3) To provide comparative cohorts to enhance analysis and broader interpretation of results.

3.1.2. Ethical Considerations and Consent

Prior ethical approval for this study was obtained from the Health Research Authority Yorkshire and Humber ethics committee (REC reference number 16/YH/0035). All participants received a study participation information leaflet and cover letter alongside the questionnaire to complete at home. Written consent was not required as appropriate completion and return of the survey implied adequate consent, in line with Health Research Authority guidance (191).

3.2. Methods

This piece of work forms part of a concurrent mixed methods study, using quantitative and qualitative (chapter 2) data collection tools, to explore the potential impact of BO on patients HRQOL. This quantitative, multicentre, self-administered questionnaire study aimed to explore the prevalence of HRQOL detriments in patients undergoing BO surveillance and DBO treatment. Participants were recruited from three NHS hospitals within the North West of England, two of which provide ET for DBO. Simultaneous data was collected from two other population cohorts including; GORD/Dyspepsia and colonic polyps requiring surveillance.

3.2.1. Participant Groups and Recruitment

All participants who completed this one-off questionnaire, were >18 years old with no upper age limit. Those recruited in person were instructed, where possible, to complete the survey at home at a time independent (>4 weeks) of a hospital appointment in order to minimise any acute impact on their responses.

- **Non-dysplastic Barrett's oesophagus**. All patients enrolled in surveillance who have a diagnosis of BO irrespective of current histology. A lack of intestinal metaplasia on most recent histology was not a criterion for exclusion providing future surveillance was planned. Patients were identified from endoscopy booking databases or outpatient clinic and recruited, when possible, via postal invite at a time independent of their surveillance test.

- **Barrett's oesophagus with dysplasia or early OAC.** Patients who had previously undergone ET for DBO (low grade dysplasia, high grade dysplasia and indeterminate for dysplasia) or BO with early OAC now undergoing surveillance. These patients were identified and recruited from two tertiary treatment centres within the North West of England (Salford Royal Foundation Trust and Central Manchester Foundation Trust). Recruitment followed two strategies. Patients were identified via local endoscopy surveillance databases and invited to complete the questionnaire via post or during a routine hospital appointment (clinic or endoscopy) and recruited in person.
- **Gastroesophageal reflux disease/Dyspepsia**. Included participants without BO who have been diagnosed with any of the following in primary or secondary care; "gastroesophageal reflux with oesophagitis", "gastroesophageal reflux without oesophagitis", "gastroesophageal reflux disease", "GORD", "acid reflux", "heartburn" or "dyspepsia". These participants have a similar symptom paradigm to BO patients with significantly less cancer risk (192). This cohort was chosen to help determine whether detriments to HRQOL in BO patients are symptom related or perhaps due to other factors. Participants were recruited from both primary and secondary care. Primary care participants were identified and invited postally from a single GP surgery. Secondary care participants were identified via hospital coding systems and postally invited or identified at the time of a hospital appointment (clinic or endoscopy) and recruited in person.
- **Colonic polyp surveillance**. Participants undergoing endoscopic surveillance for colonic adenomas without a concurrent diagnosis of BO. These patients also have a chronic precancerous condition requiring endoscopic surveillance at similar time intervals to BO patients (193). Those undergoing surveillance solely due to a personal history of colorectal cancer (CRC), inflammatory bowel disease or family history of CRC were not included. All participants were recruited via postal invite or in person in the outpatient clinic.

3.2.2. Clinical data captured

- **All participants**
    - Demographics; Age, sex, family history, carer status, employment status, smoking status, PPI usage, antidepressant usage.
    - Co-morbidities
- **Non-dysplastic BO**
    - Prague classification.
    - Timing of prior and next surveillance endoscopy.
    - Timing of previous BO clinic attendance.
- **Colonic polyp surveillance**

- BSG colonic polyp risk stratification (supplementary appendix figure 8.2.1-1)
- Timing of prior and next surveillance endoscopy.

- **Gastroesophageal reflux disease/Dyspepsia**
  - Timing of prior endoscopy, if undertaken.
  - Findings at prior endoscopy (e.g. erosive GORD, non-erosive GORD +/- other confounding findings)
- **Dysplastic BO post endoscopic therapy**
  - Prague classification and histological grade pre-ET.
  - ET modality; Radio-frequency ablation, endoscopic resection (endoscopic mucosal resection or endoscopic submucosal dissection) or argon plasma coagulation (APC).
  - Number of endoscopic therapy sessions required.
  - Time since completing successful endoscopic therapy.
  - Timing of prior and next surveillance endoscopy.
  - Timing of previous BO clinic attendance.

3.2.3. HRQOL Instruments; Scoring and Data Management

Based on previous qualitative research (chapter 2) and literature review (chapter 1) the following self-administered instruments were chosen (156,189);

The Short Form 36 (36 items, 8 domains)

The SF-36 measures generic HRQOL allowing comparison between different diseases and the general population (35). It is the most extensively used and validated generic measure across many populations. The score is subdivided into eight domains: physical functioning (PF), role limitations-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE) and mental health (MH). Summary physical and mental scores are also calculated. Used in isolation it has the potential to miss significant disease specific factors. For example in a study of IBS patients clinically important factors concerning upper gastrointestinal symptoms, musculoskeletal symptoms, sleep and sexual dysfunction went unrecognised (38).

SF-36 Norm based scoring

Raw scores of SF-36 are initially converted to 0-100 scores, with higher scores indicating better HRQOL. Comparing population samples using the original 0-100 scoring metric has led to misinterpretation of peaks and troughs due to differences in the ceilings and floors of the scales. In particular general health (GH), energy and vitality (VT) and mental health (MH) measure wide score ranges and set the ceiling relatively high by measuring very favourable levels of those domains

(194). In comparison physical functioning (PF) and role limitations physical (RP) measure a narrower range based on a lower ceiling, therefore the most favourable levels (a score of 100) represents an absence of limitations rather than well-being. Therefore, significant differences can occur between the domain 0-100 scores irrespective of the population in question leading to misinterpretation (195).

General population norms offer an answer to this by providing meaningful comparisons across scales and a more robust interpretation of disease impact. For example, the general population norm for PF is 80-90 compared to VT which is around 60. Conversion of 0-100 scores into T scores (norm-based scores) with a mean of 50 and standard deviation of 10 also allows easier interpretation without cross referencing to norm tables. The further a score is from the mean the greater the likelihood it is above or below the average for that domain. Generally speaking for interpretation of groups, a deviation from the mean (50) of 3 points (0.3 standard deviations) is deemed clinically significant (195).

Mental component summary (MCS) and physical component summary (PCS) scores are weighted to reflect correlations with all 8 health domains. They are calculated using factor score co-efficient from prior normative data (196,197). Once again, population based co-efficient can be used although prior research has shown very similar outcomes when comparing US and UK co-efficient in both cross sectional and longitudinal surveys (198).

However, the use of previously published norms also has a number of potential issues. Firstly, the most widely used norms, particularly in the UK, have been conducted in the 1990's (199-201) and 2000's (140,202). These norms will therefore not reflect subsequent changes in national socioeconomic inequalities, health and life expectancy for example (203). Secondly, when conducting a regional study ideally a regional norm should be used. Prior studies have shown significant differences in regional HRQOL data, although the reasons for this have not always been clear (200,204). Unfortunately, adequately numbered regional norms remain sparse. Thirdly, HRQOL output is influenced by age, gender and socioeconomic status (205). Therefore, one must also consider whether a particular norm adequately measures these variabilities. For example, the Oxford Healthy Life Survey, one of the most widely used UK norms had an upper age cut off of 64 years (199). Fourthly, the mode of questionnaire administration also differs amongst norms and may influence the data captured. For example, interview captured data compared to self-completed methods may introduce social desirability bias (206-208). Perkins and Sanson-Fisher found higher mean scores via interview administration, in particular in mental dimensions scores (209). This may be because participants are less likely to disclose sensitive information during an interview. Fifthly, some have postulated but not proven that the order in which the SF-36 is placed with simultaneous questionnaires may impact the scores (210). Finally, and arguably the greatest

limiting factor is the availability of norm data. Many publications provide inadequate information to facilitate further use such as missing standard deviations, age and gender breakdowns, socioeconomic groupings and prevalence of confounders such as co-morbidities.

SF-36 Data Management

All individual respondent 0-100 dimension scores in this study were converted to an age and sex matched z scores for each domain using a previously published UK norm (200) (UK omnibus sample). This national sample was chosen due to the availability, completeness of data and inclusion of older age ranges. Z scores for all domains were then converted to t scores to give a mean of 50 and standard deviation of 10.

- *e.g. Physical Functioning z score = (PF - UK norm mean)/standard deviation of UK norm.*
- *e.g. Physical Functioning t score = 50 + (PFz x 10)*

Subsequently the MCS and PCS scores were calculated using previously published UK mental and physical factor co-efficient data (198). To achieve this, aggregate MCS and PCS scores are calculated first. Part of this equation can be seen below;

- *Aggregate MCS= (PFz x factor coefficient) + (MHz x factor coefficient) + …….*

The aggregate MCS and PCS scores were then converted to t scores in the same manner as before. Please note, as per SF-36 author guidelines, in order reach a summary score 7 out of 8 domains must be available with MH present for MCS and PF present for PCS score to be valid (195).

The Cancer Worry Scale (6 Domains, 4-point Likert Scale) + Perceived risk of cancer (7-point Likert scale).

The cancer worry scale (CWS) is a 6-item score originally designed to measure cancer specific worry and impact of worry on daily functioning among women at risk of breast and ovarian cancer (211). Subsequently it has been successfully used in assessing fear of developing cancer or cancer recurrence in breast, ovarian and bowel cancer settings (79,212,213). This worry score was chosen because it encompasses both the frequency and severity of worry which are considered the most significant factors when assessing this trait (68,69).The wording of the items can also be easily modified to assess other cancer groups (214). In this study participants were asked in relation to the cancer specific to their diagnosis. The score uses a 4-point Likert scale between “Never” (1 point) and “almost always” (4 points). Total scores therefore range between 6 and 24 with higher scores indicating worse cancer specific worry. Recent re-validation was undertaken by Custers and colleagues who investigated the use of the CWS as a screening tool and provided useful score cut offs via ROC analysis against the fear of cancer recurrence inventory (RCRI). RCRI is a valid and reliable 42 item multidimensional measure of fear of cancer recurrence (FCR). Based on the highest

proposed RCRI cut off to detect "severe" levels of FCR as the gold standard the optimal CWS cut off was 11 vs 12 (sensitivity 88%, specificity 81%, NPV 97%, PPV 46%). When using a slightly less stringent RCRI cut off to detect "high" levels of FCR the optimal CWS cut off was 9 vs 10 (sensitivity 88%, specificity 73%, PPV 70%, NPV 90%) (215). For the purposes of this study the following cut offs were adopted; <10 as negative, 10-11 as borderline and ≥12 as positive. This score was accompanied by an assessment of both numerical and perceived risk of developing cancer using a 7-point Likert scale.

Hospital Anxiety and Depression Score (2 Domains, 14 items, 4-point Likert scale)

The hospital anxiety and depression score (HADS) is the most extensively used and validated screening tool for anxiety and depression (93,94,216). It has been used in a variety of healthcare settings including cancer patients (92). The HADS consists of 14 items, 7 relating to anxiety and 7 relating to depression symptoms. Items are ranked on a 4-point Likert scale between 0 and 3 with higher scores relating to more severe anxiety or depression. The sum of these items produces a HADS anxiety (HADS A) and HADS depression (HADS D) total score. The author proposed cut off points for these scores are; 0-7 suggests the absence of anxiety and depressive symptoms, 8-10 indicates the presence of symptoms to a moderate degree with doubtful cases, ≥11 indicates significant symptoms which correspond to confirmed cases (216). These thresholds were found to be robust on further scrutiny and have therefore been adopted in this study (217).

The Gastrointestinal Symptom Rating Scale (15 items, 5 Domains, 4-point Likert Scale)

The Gastrointestinal symptom rating scale (GSRS) consists of 15 items producing 5 gastrointestinal domains (abdominal pain, reflux, indigestion, diarrhoea and constipation). This extensively used symptom specific score measures frequency, intensity, duration and impact on daily life. It can identify clinically important change and discriminates well between each domain, most markedly in reflux and indigestion (42,218)**.** This study adopted a 4-point Likert scale with higher scores indicating worse symptoms (0= None, no symptoms or very rarely, 2= mild, occasional or mild symptoms, 2= moderate, frequent symptoms that impact on some social activities, 3= severe, continuous symptoms that impact most social activities). There are no defined score cut offs.

Burden of endoscopy

The acute physical and psychological stresses associated with undergoing BO surveillance endoscopy were identified and explored in depth within the qualitative methodologies (chapter 2).

The short term impact of cancer screening and surveillance on HRQOL is also well documented (60), including previous quantitative studies in non-dysplastic BO surveillance cohorts (66). This study has therefore been designed to assess patients at a time independent of their surveillance endoscopy.

3.3. Statistical analysis

HRQOL outcomes are multidimensional with no single identifiable endpoint. Therefore, analysis of all questionnaire subcategories was performed to identify any particular impacts of disease. Fisher's exact test was used to identify associations between questionnaire items and diagnostic groups. Further analysis examined for differences between diagnostic groups with propensity score matching adjusting for potential confounders. Within this analysis, individuals were matched over the estimated probability of being at the diagnostic group, called propensity score, adjusted for sex, age and comorbidities (219). Thus, individuals with the same propensity score have similar baseline observed characteristics, i.e. age, sex and co-morbidities. A sensitivity analysis to ensure the results of propensity matching score were consistent was implemented using nearest neighbour matching, where the closest individuals were matched according to a pre-defined distance (220) (please see supplementary USB appendix 9.2.1 for nearest neighbour matching tables). Finally, Fisher's exact and Spearman's rank correlation tests were performed to examine for possible associations between variables, i.e. test for association between reflux symptoms and worry of oesophageal cancer or HADS anxiety.

Cases that were incomplete in all the items of a questionnaire were excluded from the analysis of this questionnaire only. Missing values were given the mean response of each item, while the missing responses for each item was not higher than 10%. All statistical analyses were performed using Stata version 15 (221)

3.4. Results

3.4.1. Data Quality

There are a number of measures of data quality researchers can deploy when reporting the SF-36 (195) . The metrics reported in this study include: 1) Completeness of data, this is the percentage completed of the total number of possible responses. A score of ≥90% is deemed satisfactory, this study achieved >95%. 2) Consistency of responses, this can be obtained by calculating the percentage of the respondents with a response consistency index (RCI) of 0. The RCI is a measurement of the consistency of each individual respondent, a score of 0 means there were no contradicting responses in all 36 questions. Typically, ≥90% of respondents with an RCI of 0 is deemed satisfactory, this study achieved 89%. 3) Percentage of estimable scores calculable, there

are a total of 10 estimable scores for each participant (8 domains and 2 summary scores). A total of ≥90% is deemed satisfactory, this study achieved 98%. 4) Scale reliability (Cronbach's alpha), was calculated for all 8 SF-36 health domains and the other questionnaires. A satisfactory alpha is considered ≥0.7 {Tavakol:2011ft}. All instruments used in this study demonstrated excellent reliability with Cronbach's alpha ranging between 0.85 and 0.97 (supplementary appendix table 8.2.2-1)

3.4.2. Response rates and Demographics.

1740 individuals were invited to participate across all groups with an overall response rate of 39.4% (figure 3.4.2-1). The relatively low response rate likely reflects the use of postal invitation and the length of the survey. Responder versus non-responder characteristics for the BO group can be seen in table 8.2.2-2 in the supplementary appendix. This data suggests the non-responder group have fewer co-morbidities, however this may be due to differences in recording than a true difference between the groups. Co-morbidities for the responders were self-reported and obtained via clinical coding databases whereas the non-responders were identified from coding alone. Participant demographics for all 4 groups is displayed in table 3.4.2-1. A further breakdown of comorbidity prevalence and subcategories can be found in the supplementary appendix table 8.2.2-3.

Figure 3.4.2-1 Response rates

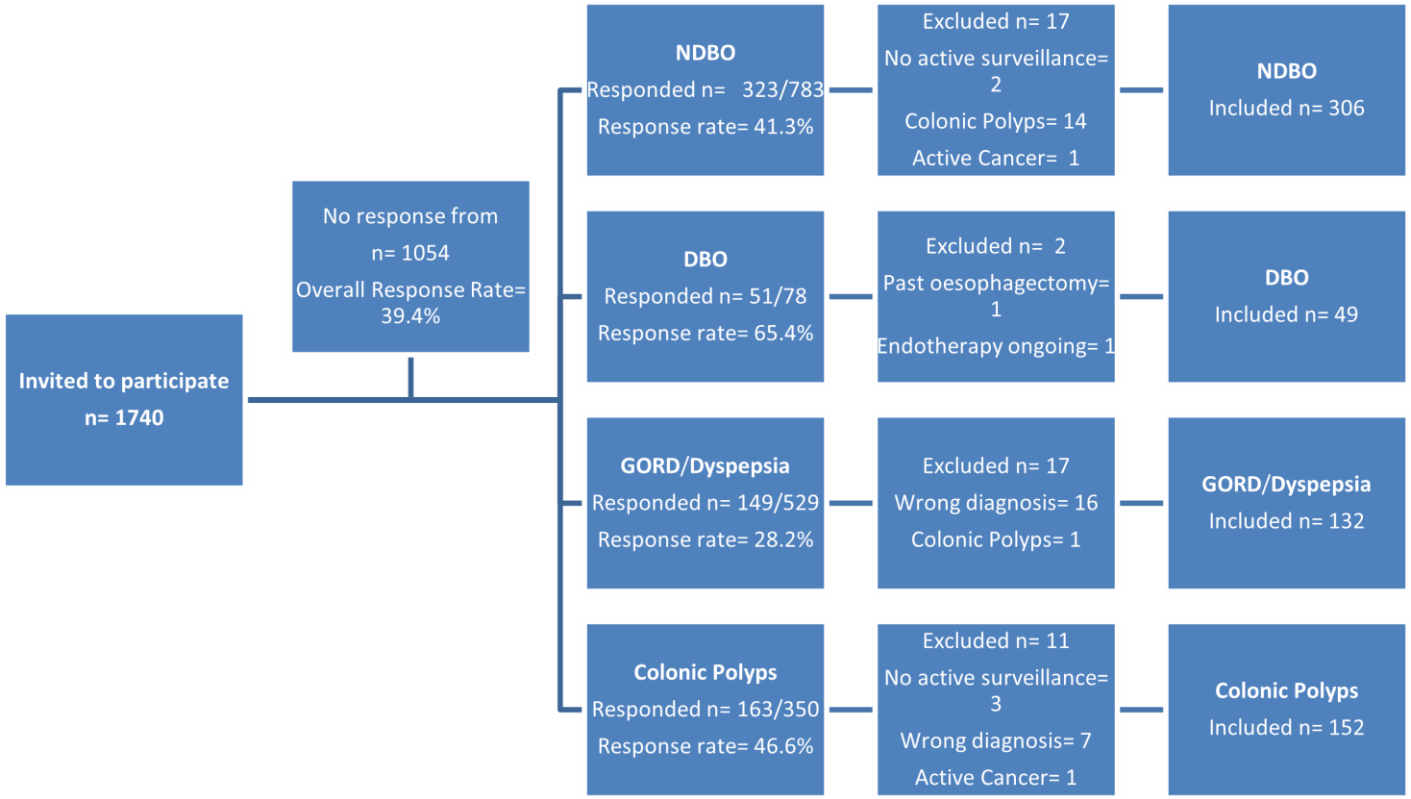


Table 3.4.2-1 Participant Demographics

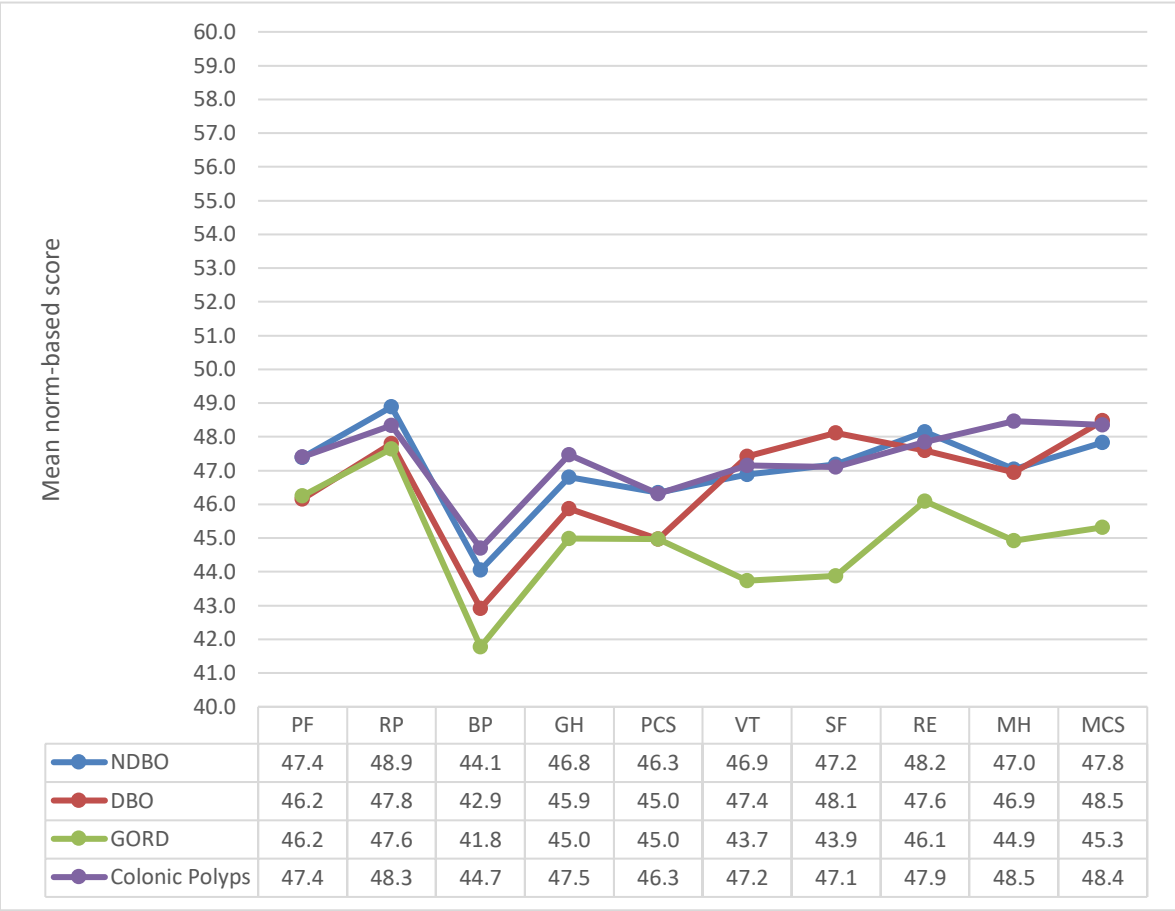
		NDBO N= 306	**DBO N= 49**	**GORD/ Dyspepsia N= 132**	**Colonic polyp N= 152**
Age	Mean Range	64.6 26-85	71.0 55-84	60.9 30-90	68.6 48-89
Sex	Male Female % Male	198 108 64.7%	44 5 89.8%	72 60 60.9%	100 52 65.8%
Employment status	Employed Unemployed Retired	32.7% 6.7% 60.6%	8.2% 0.0% 91.8%	35.9% 10.9% 53.1%	17.3% 2.7% 80.0%
Family History	Cancer Disease specific cancer Chronic disease	20.6% 7.2% (OAC) 15.4%	24.5% 2% (OAC) 16.3%	27.8% 5.4% (OAC) 21.5%	16.9% 22.5% (CRC) 13.9%
Carer	Yes	6.9%	14%	13.2%	11.3%
Smoking	Never Current Ex-smoker	43.3% 11.1% 45.6%	26.5% 4.1% 69.4%	49.6% 11.6% 38.8%	39.7% 10.6% 49.7%
PPI usage	Yes	95.1%	100.0%	84.6%	45.7%
Antidepressant usage	Yes	8.5%	10.2%	18.3%	10.6%
Prague M classification	Mean	3.6	3.9	NA	NA
Co-morbidity prevalence	None 1-2 3-4 >4	29.4% 54.2% 16.0% 0.3%	14.3% 59.2% 22.4% 4.1%	25.0% 55.3% 17.4% 2.3%	21.7% 57.9% 17.1% 3.3%

3.4.3. Generic Health Related Quality of Life (SF-36)

The mean norm-based scores, calculated against an age and sex matched UK population norm, are depicted in figure 3.4.3-1. All groups showed detriments across the physical domains, in particular bodily pain, resulting in physical component summary scores below the population norm (BO= 46.9, DBO= 45.0, GORD/Dyspepsia= 45.0 and colonic polyps= 46.3). The GORD/Dyspepsia group were also below the general population average for all 4 mental health domains culminating in the only disease group to record an MCS score below average (GORD/Dyspepsia MCS= 45.3) (figure 3.4.3-1, table 3.4.3-1).

Although this data gives an insight into generic HRQOL measures in relation to a previously published UK population cohort, it does not deliver any information to how the BO group compares in relation to the other cohorts and it remains unclear whether the generic HRQOL detriments seen here are due to the disease in question or other confounding factors such as comorbidities. In order to provide some insight into this, propensity score analysis was conducted where individuals of each diagnostic group were matched in regards to confounding factors and all groups were compared to the non-dysplastic BO cohort to look for significant differences in each domain. A p value of <0.05 accompanied with a coefficient of +/- 3 or more was considered clinically significant (195). The BO cohort had significantly higher (better) scores in the general health domain than the DBO cohort (Coef=4.3, 95% CI=[0.9, 7.6], P=0.014). Otherwise the domain and summary scores were statistically comparable to all 3 groups. This suggests that initial observed differences in the mean scores between the groups may be related to confounders than the disease in question. For example, the BO cohort had mean scores >3 in both the energy and vitality and social functioning domains when compared to the GORD/Dyspepsia group. However, after propensity score matching analysis the coefficients were only +1.2 and +0.7 respectively. Table 3.4.3-1 shows the co-efficient, 95% confidence intervals and p values after propensity score matching for age, sex and co-morbidities.

Figure 3.4.3-1 SF-36 Norm Based Scores



	PF	RP	BP	GH	PCS	VT	SF	RE	MH	MCS
NDBO	47.4	48.9	44.1	46.8	46.3	46.9	47.2	48.2	47.0	47.8
DBO	46.2	47.8	42.9	45.9	45.0	47.4	48.1	47.6	46.9	48.5
GORD	46.2	47.6	41.8	45.0	45.0	43.7	43.9	46.1	44.9	45.3
Colonic Polyps	47.4	48.3	44.7	47.5	46.3	47.2	47.1	47.9	48.5	48.4

PF Physical Functioning, RP Role Limitations Physical, BP Bodily Pain, GH General Health, PCS Physical Component Summary Score, VT Energy and Vitality, SF Social Functioning, RE Role Limitations Emotional, MH Mental Health, MCS Mental Component Summary Score.

Interpretation; Norm based scores give a direct comparison to a general population norm without having to cross reference to norm values. The scores for all groups have been age and sex matched to a prior UK general population norm. A score of 50 with a deviation of +/-3 points (47-53) is considered comparable to the general population. Lower scores (<47) indicate worse HRQOL whereas higher scores (>53) indicate better HRQOL than the general population.

Table 3.4.3-1: SF-36 norm-based scores with propensity score matching analysis

	NDBO Mean (SD) N=303	DBO Mean (SD) N=49	NDBO – DBO Coefficient (95% CI)	NDBO – DBO p value	GORD/Dyspepsia Mean (SD) N=131	NDBO – GORD/Dyspepsia Coefficient (95% CI)	NDBO – GORD/Dyspepsia p value	Colonic Polyps Mean (SD) N=151	NDBO – colonic polyps Coefficient (95% CI)	NDBO – colonic polyps p value
PF	47.4 (12.1)	46.2 (11.8)	2.9 [-3.0, 8.7]	0.337	46.2 (13.4)	-2.8 [-5.1, -0.6]	0.014*	47.4 (10.6)	0.2 [-2.0, 2.5]	0.826
RP	48.9 (8.2)	47.8 (7.7)	1.2 [-2.5, 4.8]	0.54	47.6 (9.1)	-0.4 [-2.1, 1.3]	0.651	48.3 (7.9)	0.4 [-1.5, 2.3]	0.69
BP	44.1 (10.4)	42.9 (10.7)	3.4 [-0.9, 7.7]	0.12	41.8 (10.0)	-0.3 [-2.3, 1.7]	0.777	44.7 10.5)	-0.8 [-3.4, 1.7]	0.522
GH	46.8 (10.0)	45.9 (9.5)	4.3 [0.9, 7.6]	0.014*	45.0 (10.7)	-0.9 [-3.0, 1.2]	0.41	47.5 (10.2)	-0.8 [-3.2, 1.6]	0.526
PCS	46.3 (10.7)	45.0 (10.1)	2.5 [-3.1, 8.2]	0.383	45.0 (11.0)	-2.2 [-4.2, -0.2]	0.028*	46.3 (10.3)	-0.2 [-2.3, -1.8]	0.821
VT	46.9 (9.7)	47.4 (8.6)	2.1 [-3.0, 7.3]	0.415	43.7 (11.3)	1.2 [-0.9, 3.3]	0.265	47.2 (9.4)	-0.2 [-2.7, 2.2]	0.862
SF	47.2 (11.2)	48.1 (9.6)	3.5 [-1.5, 8.6]	0.17	43.9 (13.4)	0.7 [-1.9, 3.2]	0.609	47.1 (10.5)	0.5 [-2.1, 3.0]	0.723
RE	48.2 (9.1)	47.6 (47.6)	0.9 [-2.3, 4.1]	0.586	46.1 (10.8)	0.3 [-1.7, 2.4]	0.75	47.9 (8.6)	-0.2 [-2.2, 2.0]	0.872
MH	47.0 (10.5)	46.9 (10.5)	2.8 [-3.6, 9.1]	0.397	44.9 (12.3)	1.1 [-1.5, 3.6]	0.41	48.5 (9.9)	-1.1 [-3.6, 1.5]	0.411
MCS	47.8 (9.5)	48.5 (9.0)	1.0 [-4.4, 7.6]	0.607	45.3 (11.4)	1.4 [-1.2, 4.0]	0.288	48.4 (8.4)	-0.6 [-2.8, 1.6]	0.599

This table compares the norm-based scores of all groups to the non-dysplastic BO cohort using propensity score matching for age, sex and comorbidities. P values are derived by Fisher's exact test.

3.4.4. Gastrointestinal Symptoms (GSRS)

The majority of the non-dysplastic BO cohort reported good reflux symptom control with only 11% reporting moderate or severe heartburn and 10% reporting moderate or severe acid regurgitation. These rates were statistically comparable to the treated DBO cohort. When compared to GORD/Dyspepsia patients, non-dysplastic BO participants had significantly better reflux control with 31.3% (p=<0.001) and 25.2% (p=0.001) of GORD/Dyspepsia participants reporting moderate

to severe heartburn or acid regurgitation respectively (table 3.4.4-1). These findings were reproduced when comparing the two groups reflux domain score (combined heartburn and acid regurgitation items) with propensity score matching analysis (table 3.4.4-2). GORD/Dyspepsia participants also exhibited other significant gastrointestinal symptoms when compared to non-dysplastic BO participants, i.e. increased nausea (p=<0.001), belching (p= p=<0.001), flatus (p=0.002) and harder stools (p=0.004). This finding is supported by a significantly greater gastrointestinal symptom total mean score after propensity score matching analysis (p=0.012) (table 3.4.4-2). As expected, the colonic polyp patients displayed significantly fewer upper gastrointestinal symptoms (abdominal pain p=0.006, reflux p=0.001, and indigestion p=0.047 domains) but were comparable in terms of lower gastrointestinal symptoms with the non-dysplastic BO patients. (Table 8.2.2-4, in the supplementary appendix, presents the frequencies and percentages for each group and item.)

Table 3.4.4-1; Gastrointestinal symptom rating scale. Moderate or Severe symptoms (15 items).

	NDBO N= 305	**DBO N= 48**	**GORD/Dyspepsia N=131**	**Colonic Polyp N=150**
1) Abdominal pains	**13.2% (39)**	9.1% (4) p=0.208	19.5% (24) p=0.126	10.1% (14) p=0.073
2) Heartburn	**11.2% (33)**	2.2% (1) p=0.172	31.3% (40) p=<0.001*	6.3% (9) p=0.011*
3) Acid Regurgitation	**10.0% (30)**	4.3% (2) p=0.31	25.2% (32) p=0.001*	2.8% (4) p=<0.001*
4) Hunger Pains	**9.5% (28)**	6.7% (3) p=0.349	15.1% (19) p=0.311	2.8% (4) p=0.013*
5) Nausea	**3.7% (11)**	2.2% (1) p=0.125	7.1% (9) p=<0.001*	0.0% (0) p=0.009*
6) Rumbling	**10.4% (31)**	4.7% (2) p=0.031*	11.7% (15) p=0.148	8.3% (12) p=0.187
7) Abdominal Bloating	**16.6% (49)**	6.7% (3) p=0.053	18.0% (23) p=0.553	9.0% (13) p=0.097
8) Belching	**11.1% (33)**	6.5% (3) p=0.63	25.6% (33) p=<0.001*	2.1% (3) p=<0.001*
9) Increased Flatus	**14.0% (42)**	15.2% (7) p=0.581	27.5% (36) p=0.002*	8.9% (13) p=0.417
10) Decreased Stools	**25.5% (73)**	19.1% (9) p=0.433	31.5% (40) p=0.014*	21.6% (30) p=0.771
11) Increased Stools	**5.9% (17)**	8.5% (4) p=0.193	5.5% (7) p=0.323	4.3% (6) p=0.85
12) Loose Stools	**6.8% (20)**	4.4% (2) p=0.357	9.8% (12) p=0.044*	6.3% (9) p=0.391
13) Hard Stools	**9.5% (28)**	8.9% (4) p=0.715	17.1% (21) p=0.004*	9.1% (13) p=0.737
14) Urgency	**8.5% (25)**	11.1% (5) p=0.572	8.9% (11) p=0.207	7.0% (10) p=0.752
15) Incomplete Evacuation	**10.9% (32)**	4.4% (2) p=0.157	16.3% (20) p=0.049*	7.7% (11) p=0.539

This table compares all groups to the non-dysplastic BO cohort for each item of the GSRS. P values are derived by Fisher's exact test for association.

Table 3.4.4-2; Gastrointestinal symptom rating scale domain scores

	NDBO **Mean**	**DBO** Mean P value	**NDBO - DBO** Coefficient (95% CI)	**GORD/Dyspepsia** Mean P value	**NDBO - GORD/Dyspepsia** Coefficient (95% CI)	**Colonic polyp** Mean P value	**NDBO - Colonic Polyp** Coefficient (95% CI)
Abdominal Pain Domain	**1.08**	0.67 P=0.174	0.253 [-0.112, 0.618]	1.57 P=0.366	-0.171 [-0.541, 0.199]	0.68 P=0.006*	0.424 [0.12, 0.729]
Reflux Domain	**1.01**	0.65 P=0.168	0.497 [-0.21, 1.205]	1.85 P=0.004*	-0.63 [-1.064, -0.197]	0.53 P=0.001*	0.463 [0.202, 0.724]
Diarrhoea Domain	**1.00**	1.15 P=0.693	-0.114 [-0.681, 0.453]	1.28 P=0.598	-0.095 [-0.449, 0.259]	0.89 P=0.632	0.097 [-0.3, 0.495]
Indigestion Domain	**2.38**	1.85 P=0.882	-0.104 [-1.479, 1.271]	3.30 P=0.071	-0.527 [-1.1, 0.046]	1.68 P=0.047*	0.525 [0.008, 1.043]
Constipation Domain	**1.77**	1.70 P=0.583	-0.329 [-1.502, 0.844]	2.56 P=0.084	-0.439 [-0.938, 0.059]	1.54 P=0.765	-0.061 [-0.461, 0.339]
GSRS Total Score	**7.17**	6.00 P=0.815	0.314 [-2.319, 2.948]	10.42 P=0.012*	-1.785 [-3.179, -0.389]	5.29 P=0.015*	1.538 [0.293, 2.783]

This table compares all groups to the non-dysplastic BO cohort for the 5 domain scores and overall score using propensity score matching. P values are derived by Fisher's exact test. Note higher scores indicate worse symptoms and comparisons between domains are not possible as the number of items which makes up each domain is variable.

3.4.5. Cancer worry

A substantial proportion of non-dysplastic BO participants reported significant worry regarding oesophageal cancer with 53% recording positive and 17% borderline CWS. This finding was similar to those treated for DBO (p=0.933) and participants undergoing colonic polyp surveillance (p=0.355) when questioned regarding colorectal cancer. GORD/Dyspepsia participants reported significantly less oesophageal cancer worry compared to non-dysplastic BO participants (p=0.01), however 43% still reported a positive CWS (table 3.4.5-1). This finding is despite 83% (n=109/132) of GORD/Dyspepsia participants having undergone a prior reassuring and relatively recent (mean 0.9 yrs.) gastroscopy. (Table 8.2.2-5 in the supplementary appendix displays the frequencies and percentages for each item across all groups).

Table 3.4.5-1 Cancer worry scale. (total mean and categorical)

	Total Mean (SD)	**Category % Normal (<10)**	**Category % Borderline (10-11)**	**Category % Positive (≥12)**	**NDBO vs P value**
NDBO	**12.35 (4.51)**	**30.5% (91)**	**16.8% (50)**	**52.7% (157)**	
DBO	12.67 (4.95)	33.3% (16)	16.7% (8)	50.0% (24)	P=0.933
GORD/Dyspepsia	10.88 (4.98)	45.7% (59)	10.9% (14)	43.4% (56)	P=0.01*
Colonic Polyp	11.58 (3.93)	36.2% (54)	12.8% (19)	51.0% (76)	P=0.355

This table compares all cohorts to the non-dysplastic BO group using the CWS categories; normal, borderline and positive. P values are derived by Fisher's exact test.

3.4.6. Cancer risk perception

The annual incidence of disease progression with BO is between 0.2-0.4% compared to that of disease recurrence in ET treated DBO of 1-2% (6,101,222,223). Based on this, the majority of the BO cohort either underestimated (43%) or overestimated (34%) their numerical 1-year risk, leaving only 22% who correctly chose either 1 in 500 or 1 in 250. DBO participants tended to under (75%) rather than over (8%) estimate their numerical risk of disease recurrence with only 18% choosing appropriately. Table 3.4.6-1.

However, an accurate understanding of numerical risk may not be important for patients or indeed correlate with their perception of risk. The corresponding items on the perceived risk scale show a greater percentage of BO and DBO patients who perceive their risk more accurately (32% in both groups). If "very small" is also included in this calculation for non-dysplastic BO patients then this

increases to 59% (n=169) of patients who selected the lower end of the scale and fundamentally perceive their risk as “small”. The result produced by the same calculation for the DBO group is comparable (n=27, 61%), suggesting they have a similar risk perception of OAC as patients who have never had dysplasia. Numerical and perceived risk scales correlated with each other across 3 of the 5 diagnostic groups (BO, DBO and colonic polyps).

The incidence of OAC in GORD is well established (192,224), although substantially lower than in BO cohorts. Prior research estimates the incidence of OAC in males aged 65 years with daily reflux is 74.7/100,000 per annum. This risk drops off significantly below the age of 55 and is even lower in females. In fact, the risk of OAC in females with GORD is lower than that of males without GORD (224). Despite this, this study has found many GORD/Dyspepsia patients worry about OAC (43.4%) with 10.6% perceiving their risk as large. Likewise, the incidence of CRC in patients engaging in polyp surveillance in the UK is low (208/100,000 per year) and significantly reduced by surveillance. The risk in patients undergoing surveillance who lack high risk features (e.g. poor-quality colonoscopy, proximal polyps, high grade dysplasia or adenoma >20mm) may be comparable or lower to that of the general population (225). The majority of patients within this studies cohort were either intermediate (57%) or low (26%) risk as per current national guideline definitions (193). Despite the known protective effects of adenoma surveillance, 13.8% of participants in this study perceived their risk as large with 51% reporting a positive cancer worry score in relation to CRC.

Table 3.4.6-1 Cancer risk correlation

		NDBO n=298	**DBO n=48**	**GORD/Dyspepsia n=129**	**Colonic Polyps. n=149**
Perceived Cancer Risk	Very Small*	26.6% (77)	25.0% (11)	37.7% (46)	24.1% (35)
	Small*	20.1% (58)	22.7% (10)	14.8% (18)	15.9% (23)
	Quite Small*	11.8% (34)	13.6% (6)	18.9% (23)	17.9% (26)
	Neither Small or Large	27.7% (80)	29.5% (13)	18.0% (22)	28.3% (41)
	Quite Large^	9.3% (27)	2.3% (1)	8.2% (10)	11.7% (17)
	Large^	3.5% (10)	2.3% (1)	0.8% (1)	0.7% (1)
	Very Large^	1.0% (3)	4.5% (2)	1.6% (2)	1.4% (2)
	% perceiving their risk as "small" *	58.5% (169)	61.3% (27)	71.4% (87)	57.9% (84)
	% perceiving their risk as "large" ^	13.8% (40)	9.1% (4)	10.6% (13)	13.8% (20)
Numerical Cancer Risk	1 in 1000* (0.1%)	43.4% (125)	42.5% (17)	45.9% (56)	43.2% (60)
	1 in 500* (0.2%)	13.9% (40)	25.0% (10)	17.2% (21)	18.0% (25)
	1 in 250* (0.4%)	8.3% (24)	7.5% (3)	4.1% (5)	4.3% (6)
	1 in 100 (1%)	15.6% (45)	7.5% (3)	8.2% 10)	12.9% (18)
	1 in 50 (2%)	10.8% (31)	10.0% (4)	7.4% (9)	7.9% (11)
	1 in 25 (4%)	3.8% (11)	0.0% (0)	4.9% (6)	3.6% (5)
	1 in 10 (10%)	4.2% (12)	7.5% (3)	12.3% (12.3)	10.1% (14)
Correlation of perceived and numerical risk	Total 0.342	<0.001*	0.04*	0.235	<0.001*

P values are derived from Spearman's Correlation test.

3.4.7. Psychological Impact (Anxiety and Depression)

The prevalence of anxiety within the non-dysplastic BO cohort was 15.8% with a further 15.2% recording a borderline result. Rates of depression were lower (8.6% positive and 10.6% borderline) (table 3.4.7-1). Antidepressant usage was highest in the GORD/Dyspepsia group (18%) which is also reflected by the occurrence of mental health disorders which was highest in this cohort (33%) (supplementary appendix table 8.2.2-3). One may therefore expect significantly higher rates of anxiety and depression in this group. However, all groups were statistically comparable to the non-dysplastic BO cohort. This finding was reproduced when the HADS mean scores (HADS A mean and HADS D mean) were compared after propensity score matching analysis (p=<0.001).

Table 3.4.7-1 Hospital anxiety and depression score (Anxiety)

Group	HADS A Total Mean (SD)	PSM Coefficient (95% CI)	HADS A Mean NDBO vs Other P value	HADS A Normal %	HADS A Borderline %	HADS A Positive %	HADS A Category NDBO vs Other P value
NDBO	5.5 (4.5)			69.0% (209)	15.2% (46)	15.8% (48)	
DBO	4.7 (3.6)	-0.48 [-2.245, 1.285]	0.594	83.7% (41)	8.2% (4)	8.2% (4)	0.125
GORD/Dyspepsia	6.6 (5.0)	-0.433 [-1.53, 0.665]	0.44	64.1% (84)	13.7% (18)	22.1% (29)	0.301
Colonic Polyp	4.7 (3.9)	0.805 [-0.123, 1.733]	0.089	75.7% (112)	12.8% (19)	11.5% (17)	0.329

This table compares all groups to the non-dysplastic cohort using both mean scores, after propensity score matching, and the categorical breakdown (normal, borderline and positive). P values are derived by Fisher's exact test.

Table 3.4.7-1 Hospital anxiety and depression score (Depression)

	HADS D Total Mean (SD)	PSM Coefficient (95% CI)	HADS D Mean NDBO vs Other P value	HADS D Normal %	HADS D Borderline %	HADS D Positive %	HADS D Category NDBO vs Other P value
NDBO	4.2 (4.0)			80.9% (245)	10.6% (32)	8.6% (26)	
DBO	3.7 (3.1)	-0.015 [-1.227, 1.197]	0.981	79.6% (39)	18.4% (9)	2.0% (1)	0.094
GORD/Dyspepsia	5.5 (4.4)	-0.59 [-1.788, 0.607]	0.334	71.0% (93)	14.5% (19)	14.5% (19)	0.065
Colonic Polyp	4.0 (3.6)	0.488 [-0.414, 1.391]	0.289	83.8% (124)	8.1% (12)	8.1% (12)	0.734

This table compares all groups to the non-dysplastic cohort using both mean scores, after propensity score matching, and the categorical breakdown (normal, borderline and positive). P values are derived by Fisher's exact test.

3.4.8. Correlation of measures

Further analysis, using Fisher's exact and Spearman's correlation test, examined correlations between variables within the non-dysplastic BO cohort. BO patients who reported moderate or severe GORD symptoms (heartburn, reflux) were associated with higher rates of both anxiety (p=<0.001, p=<0.001) and depression (p=<0.001, p=<0.001). Higher (worse) scores in the reflux domain (combined items) were also associated with higher (worse) cancer worry scores (p=<0.001). Patients with higher cancer worry were associated with significant anxiety (p=<0.001) and depression (p=<0.001). Those who correctly perceived their cancer risk as low tended to have significantly lower rates of cancer worry (p=<0.001). This was also the case for numerical risk estimation (p=0.003).

3.5. Discussion

The major finding in this study was the high prevalence of OAC related cancer worry among non-dysplastic BO patients undergoing surveillance. It also appears that after ET for dysplasia or early OAC patient cancer specific worry is comparable to that of patients who have never had dysplasia. This finding is supported by the HRQOL data from the AIM dysplasia trial (85). At 12 months follow up, patients who had undergone successful RFA for DBO reported significantly less worry than those who had received a sham procedure. Interestingly this was at a time when the true efficacy of ET was unknown. It therefore appears that informing patients they no longer have dysplasia or indeed BO is very reassuring to them. These findings need further delineation with a prospective paired pre and post treatment HRQOL study. The other study concerning cancer worry and DBO treatment was conducted by Rosmolen and colleagues (190). They compared oesophageal cancer worry of endoscopically treated high grade dysplasia or early OAC to patients treated surgically in a single centre Netherlands study. Significantly higher levels of cancer worry were found in ET patients compared to surgically managed ones with similar disease stage. This may reflect the perceived risk of recurrence associated with having an intact oesophagus, especially when one considers the asymptomatic nature of disease progression. The payoff for lower levels of worry, in this surgical cohort, was significantly worse oesophageal and cancer related symptoms. This finding is supported by previous HRQOL data concerning oesophagectomy treated patients (97). It must be noted however that this study was single centre, relatively underpowered with <50 participants in each group and did not control for co-morbidities. Interestingly the authors also chose not to measure cancer worry, anxiety or depression in the non-dysplastic BO cohort as they did not expect these to be prevalent. Our study not only found prevalent oesophageal cancer worry in the non-dysplastic BO cohort but also high levels in GORD/Dyspepsia patients. This is despite a substantially lower relative risk and recent reassuring endoscopy in the majority of cases.

The anxiety and depression scores found in this study are comparable to that reported by Cooper and colleagues in a previous UK BO cohort with mean HADS A scores of 5.5 and 6.1 and mean HADS D scores of 4.2 and 4.0 respectively. The incidence of combined abnormal and borderline cases were 31% vs 39% for anxiety and 19% vs 14% for depression respectively (58). Sub analysis of the non-dysplastic BO cohort in this study, suggests that GORD symptom severity is associated with oesophageal cancer worry, anxiety and depression. The causality or direction of these associations cannot be concluded from this analysis alone. Yet, when interpreted alongside the qualitative findings in chapter 2 a greater understanding of these interactions can be achieved. The qualitative study demonstrated that, in some cases, GORD symptom flares lead to worry or anxiety regarding disease progression. Other factors also instigated in cancer worry included having dependents, an anxious predisposition and inadequate disease specific knowledge, particularly cancer risk perception (189). Indeed, perception of oesophageal cancer risk in this quantitative study correlated well with severity of cancer worry, as did numerical risk to a lesser extent.

The data captured in this study suggests symptom control for the majority of BO patients is good with around 10% reporting moderate to severe symptoms. Symptom severity is comparable to the DBO cohort, a finding consistent with that of Rosmolen and colleagues (190). GORD patients appear to have significantly worse symptoms, a finding supported by prior studies (5,53,54). There are a number of potential reasons for this. Firstly, higher rates of PPI usage in non-dysplastic BO cohorts (95.1% versus 84.6% in this study). Secondly, a significant minority of BO patients are diagnosed incidentally and have never suffered GORD symptoms. Finally, GORD cohorts may also contain more participants with functional gastrointestinal disorders. This may be the case in this study as the GORD/Dyspepsia cohort reported significantly worse gastrointestinal symptoms outside the reflux domain. Also, of those who had undergone a recent endoscopy (109/132), 46% (n=50) had non-erosive disease, 32% (n=35) had reflux oesophagitis and 22% (n=24) had dyspepsia with or without gastritis. It is worth noting that quantitative measurement of symptoms may miss important flare ups depending on the recall period of the questionnaire used. The qualitative work in chapter 2 has suggested these flares, albeit infrequent, can be disruptive for patients, difficult to manage and impact significantly on HRQOL (189).

Generic HRQOL measures (SF-36), in this study, suggest BO patients have significantly lower (worse) physical component scores, in particular bodily pain when compared to an age and sex matched UK population norm. These findings are consistent with Lippman and colleagues (53) who examined HRQOL in BO and GORD patients in a single tertiary centre in the US. Considering BO reflux symptom control is generally good, this finding is unlikely to be solely related to BO and may reflect co-morbid disease. Otherwise, using this metric alone (SF-36), BO patients could be considered to have a HRQOL close to that of the general population. This study also highlights the importance of controlling for potential confounding factors when measuring HRQOL, especially when making

comparisons between disease groups. Without adjusting for these, data can easily be misinterpreted. After adjusting for age, sex and co-morbidities this study found very few significant differences across the disease groups.

This study highlights key areas of disease impact on BO patients. These findings are important to consider when implementing BO care pathways. Considering historical BO care has been inconsistent, inadequate or non-existent (1,144,189) there needs to be a greater focus on counselling patients regarding cancer risk with perhaps an emphasis on using words rather than numerical values in explanations. Previous research has shown that patients' perception of risk, rather than knowledge of numerical risk, is what drives health behaviour and influences HRQOL (82,83). Although the majority of non-dysplastic BO patients in this study, and prior research (89), perceive their cancer risk as low there is still a significant minority who overestimate it. Lowering perceived cancer risk in these patients may in turn reduce cancer specific worry, anxiety and depression. This appears key to non-dysplastic BO patients who appear more likely to overestimate their cancer risk (34% overestimate numerical risk and 42% overestimate perceived risk) compared to treated dysplastic/OAC patients (8% overestimate numerical risk and 7% overestimate perceived risk). A prior US cohort study of non-dysplastic BO patients, conducted by Shaheen and colleagues, found even higher rates (68%) of numerical risk overestimation (88). Discussions concerning cancer risk are also important when not pursuing surveillance, for example newly diagnosed patients who do not meet current surveillance criteria. Reassurance for BO patients may also be provided by a negative surveillance endoscopy. DBO treated patients remain under greater endoscopic scrutiny, which may be one explanation as to why they have a perceived cancer risk similar to that of non-dysplastic levels. The reassuring findings of endoscopy should be communicated by the endoscopist immediately and effectively to all, including GORD and colonic polyp patients undergoing endoscopy who typically do not receive further clinic follow up. This interaction between endoscopist and patient must not be underestimated. Cooper and colleagues found lower (worse) trust in physician scores were associated with greater levels of anxiety and depression (58). Similarly physician-patient communication surrounding surveillance endoscopies has been shown to be vitally important to patients in prior qualitative work (147,189). Surveillance intervals for some patients can be long (3-5 years) and the reassurance of a negative endoscopy will naturally dwindle over time. It may therefore be appropriate to provide BO patients with a direct access to secondary care services in between their endoscopies.

This research also forms part of the preliminary work necessary to develop a BO specific PROM encompassing both non-dysplastic and dysplastic patients. Based on these findings a BO PROM must focus on GORD symptom control, perceived cancer risk and cancer specific worry. Development and validation of a BO PROM would make HRQOL research in this area less cumbersome for both participants and researchers. It would simplify instrument (questionnaire)

selection for the researcher whose background interests often lie outside HRQOL research, which is frequently a secondary or tertiary outcome measure. In turn this may provide greater consistency allowing more accurate cross trial comparisons.

3.5.1. Limitations

This study is not without limitations. Firstly, the response rate is relatively low. This may lead to significant differences between responder and non-responder characteristics introducing bias, which may reduce reliability and generalisability of the results. In view of this responder and non-responder non-dysplastic BO characteristics have been provided (supplementary appendix 8.2.2-2). Secondly, the demographics of each cohort are not perfectly matched. However, this has been accounted for within the analysis through propensity score matching which included age, sex and co-morbidities. Thirdly, colonic adenoma patients who engage with surveillance have a lower risk of colorectal cancer than the general population and are therefore not directly comparable to BO patients who have an increased risk of cancer compared to the general population. Finally, socioeconomic status was not recorded which is another potential confounding factor in HRQOL research. Despite these limitations the data captured is of good quality, multicentre and considers a range of potential disease impacts.

3.6. Conclusion

To our knowledge this study provides the largest and most comprehensive quantitative HRQOL measurement of BO patients within the NHS. Based on these findings, patients require greater reassurance and communication concerning oesophageal cancer risk. Current and future care pathways must be more patient focused with greater attention given to assessing and addressing misconceptions of cancer risk, oesophageal cancer related worry and GORD symptom control.

4. Chapter 4 - Research Priority Setting in Barrett's Oesophagus and Gastroesophageal Reflux Disease

4.1. Introduction

Research could be considered a well-established concept which aims to address important and relevant uncertainties. The question of who decides what are the key research priorities and why some areas of research receive funding and focus leaving others perhaps overlooked is somewhat less clear. Typically, research is funded by the government (public), industry (pharmaceutical and medical device companies) and charities. Past financial constraints on public research spending has historically produced strong links between academic researchers and industry (226). This has conceivably had an impact on the research areas selected. This misalignment of priorities between the researchers and research users could have serious deleterious consequences to patients, frontline staff and broader society (136,227,228). Tallon and colleagues first described this imbalance in the setting of osteoarthritis, where an inappropriate focus on drug treatments in ongoing clinical trials stood in stark contrast to results of surveys and focus groups showing that patients, rheumatologists, physiotherapists, and general practitioners all sought strengthened emphasis on research into non-drug treatments (136). To explore this further Chalmers et al examined the characteristics of non-commercially funded clinical trials between 1980 and 2002 (229). They identified two broad funding methods; 1) "Responsive Funded" trials by the MRC (medical research council) or charities after successful application by the researcher. 2) "Commission Funded" trials which reflected the priorities of the funders (e.g. Department of Health and NHS Research and Development). Trials funded in a "Responsive" manner were heavily focused on drug treatments and addressed a narrower spectrum of health problems (primarily cancer and cardiovascular disease). In comparison "Commission" funded research explored more non-drug treatments and a broader range of conditions. However, neither of these non-commercial approaches have routinely engaged with the agendas of the research user. One may expect an even poorer outlook in commercially funded research. The minority of research which did engage with patients during this timeframe had varying methodologies, levels of involvement and no clear consensus of best approaches {Oliver:2004ej}.

In an attempt to narrow the gap between the researcher and the research user there has been an increasing trend to include patients and public members when setting research agendas. The dissemination and publication of "Top 10 Research Priorities" has become a potentially powerful influence on the direction of future research (108,139). One particular, non-profit making, initiative called The James Lind Alliance (JLA) is dedicated to bringing together clinicians, patients, and carers

to discuss research priorities. These collaborations have produced over 40 priority setting publications which span variety of diseases and health-care settings (118). Their methodologies are robust, reproducible and transparent. This has been recognised by the National Institute for Health Research who now fund their infrastructure (138). These methodologies should act as a guideline for those seeking to define research uncertainties in their own field of interest (137).

Table 4.2-1 highlights the potential benefits and challenges when involving patients and the public in research priority setting or healthcare improvement (108,123,130,137,139).

Table 4.2-1 Involving Patients in Research and Healthcare Improvement Priority Setting

Advantages	• Bring patient, carers and professionals together on a level playing field. • Raise awareness of previously overlooked areas • Influence direction and funding of future research towards the interests and needs of the research user (patients, carers and frontline staff) • Potential life changing impact for patients (especially in chronic disease settings) • Mutual influence from both groups has shown professional and patient priorities move closer together during this process.
Challenges	• Research Priorities set by patients can be broad or poorly defined. • Research Priorities identified by patients may have harder research end points to achieve. For example, the impact of chronic disease on patients compared to outcomes of a drug therapy RCT. • The longer-term impact of patient involvement is hard to measure (especially at a wider population level) • Public participants may lack understanding of the scientific literature • Potential under representation of certain patient groups for example vulnerable patients or those from more disadvantaged socio-economic groups. • Patient communication, confidence and self-esteem issues may negatively impact their contributions. • Some researchers attitude to PPI are slow to change and still doubt if patients can actually influence the decisions of professionals. • Additional financial costs and greater time requirements needed to include, empower and effectively involve patients.

Despite such initiatives and longstanding government plans to involve patients in healthcare development (161) there is recent evidence to show the research landscape is slow to change (227). Worryingly in 2015 Crowe et al (228) demonstrated similar discrepancies to those first highlighted by Tallon 14 years ago. Crowe examined the JLA's first 14 publications in which drugs accounted for just 18% of the published uncertainties compared to 37% of non-commercial and 86% of commercial trials over the same time period. Nevertheless some priority setting exercises have had quite a staggering impact on the immediate direction of research (139,140).

To date is no patient-centred assessment of priorities for research in the field of Barrett's oesophagus or gastro-oesophageal reflux disease. In view of the growing incidence of these diseases, their future burden on health-care resources, and the poor advances

in oesophageal adenocarcinoma survivorship, future research efforts must be defined and focused. (155,230)

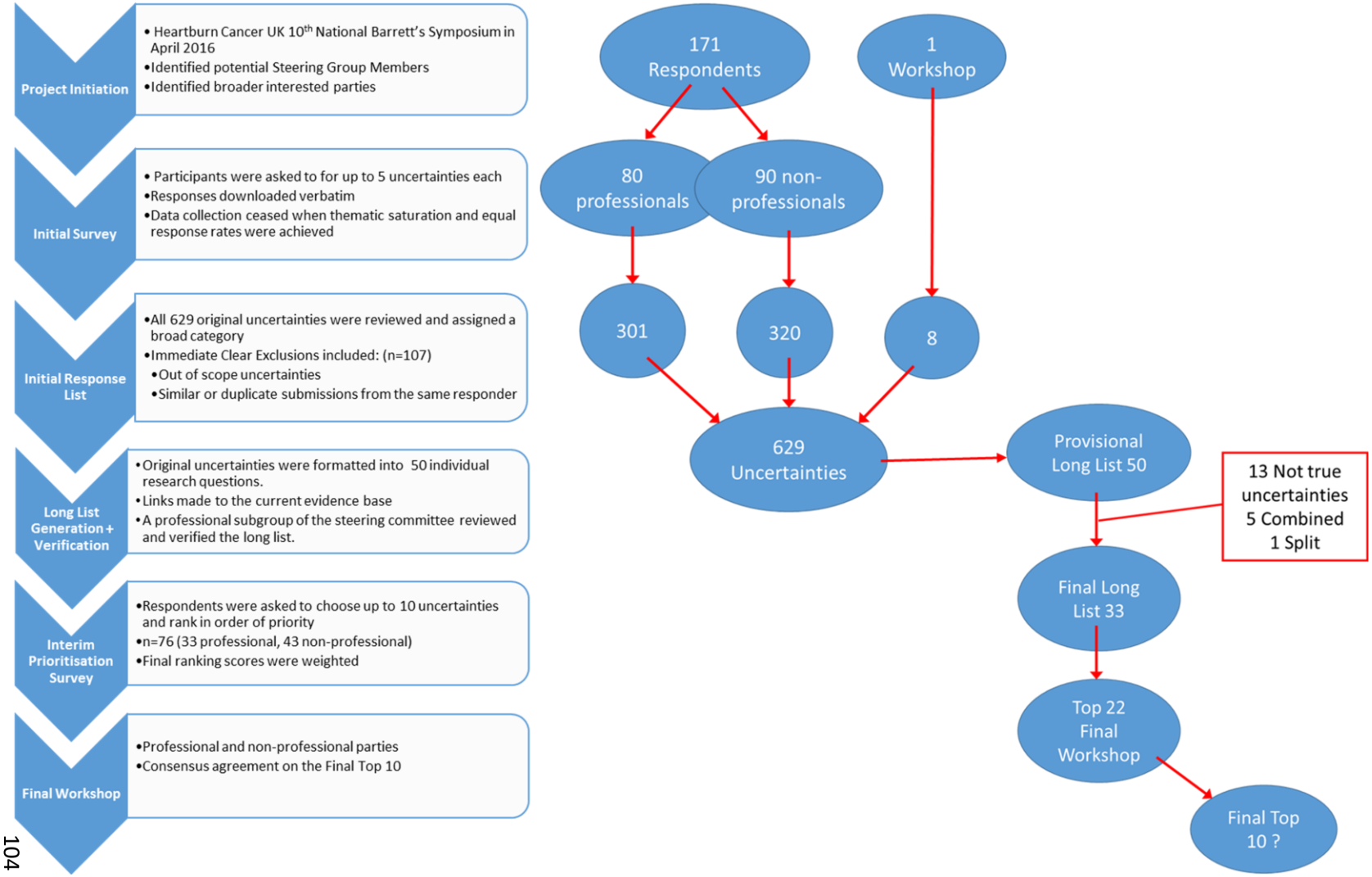
4.2. Aims

1) To facilitate a balanced patient and clinician involvement in the priority setting process.
2) To agree on a final "Top 10 Uncertainties"
3) To publish the methodology and results in a relevant open access journal.
4) Influence the direction of future research agendas

4.3. Methods

This project was led and instigated by the British Society of Gastroenterology charity CORE. CORE acted as an independent facilitator and central linchpin for all interested parties. The University of Manchester worked alongside CORE to provide an academic advisory role. The process of identifying research priorities is presented in figure 4.3-1

Figure 4.3-1 Summary of Methodology: Barrett's Oesophagus Research Priority Setting Exercise



4.4. Ethical Considerations and Data Control

In line with other research priority setting projects this research is classified as an evaluation of current service and did not require formal ethical approval. We assumed participants able to complete the questionnaire had adequate capacity and competence to be involved in the study. Responders were given the option to complete the initial survey anonymously or leave their contact details. Participants who left their contact details were then available for the subsequent rounds of the prioritisation process. All participants contact details were kept strictly confidential as per Good Clinical Practice guidelines.

4.4.1. Project Initiation and Identification of Interested Parties

The project was officially launched by CORE at the Heartburn Cancer UK 10th National Barrett's Symposium in April 2016. Symposium attendees were invited to an interactive workshop on research priority setting. This attracted a mixture of professionals, patients and associated charity representatives. The principals of research priority setting and project proposal were presented before encouraging a more interactive group discussion. This dialogue aimed to; 1) Identify key potential participants and the organisations who may have access to them (table 4.4.1-1) 2) Identify and invite a range of participants to form a steering group 3) Begin to explore some research uncertainties.

Table 4.4.1-1 Key Potential Participants Identified

Professionals	Gastroenterologists Upper gastrointestinal Surgeons Registrar trainees Nurse endoscopists and Endoscopy Nurses Histopathologists Clinical Researchers
Non-Professionals	Patients (Barrett's oesophagus, gastroesophageal reflux disease and oesophageal adenocarcinoma) Family members or friends of patients Charities
Excluded	Non-Clinical Researchers Associated industry employees (for example drug and medical device companies)

4.4.2. Data Collection: Initial Survey

Typically, previous research priority setting has focused solely on "treatment" uncertainties. Considering the comparatively narrower field of BO and GORD we opted to include all aspects of the disease paradigm. A preliminary online survey was undertaken to check feasibility of the study

and appropriateness of the responses generated before the project was formally launched (supplementary appendix 8.3.1). The online survey, open for 6 months, asked participants to enter up to 5 possible issues that they felt should be research priorities. Relevant charities and organisations were invited to help distribute the survey to non-professional groups (table 4.4.2-1). This was conducted via email to their members or by posting a live link on their website. Professional participants were contacted via their base hospital email accounts and asked to distribute the survey throughout their local departments. Regional registrar trainees were asked to participate via the North-West Gastroenterology Trainee Research Network. Data collection continued until thematic saturation was reached with equal contributions from professional and non-professional groups.

Table 4.4.2-1 Charities and Organisations Invited to Distribute the Survey

Professional	BSG - British Society of Gastroenterology AUGIS – Association of Upper GI Surgeons PCSG – Primary Care Society for Gastroenterology.
Non-Professional	CORE – Fighting Gut and Liver Disease Action Against Heartburn Barrett's Oesophagus Campaign Barrett's Wessex Cancer Research UK CARD – Campaign Against Reflux Disease FORT – Fighting Oesophageal Reflux Together Gutsy Group – Patient Support Group Heartburn Cancer UK Humberside Oesophageal Support Group Michael Blake Foundation - Oesophageal Cancer Awareness and Prevention. Oesophagoose – Oesophageal and Gastric Cancer Awareness Campaign OOSO- Oxfordshire Oesophageal and Stomach Organisation OCHRE charity – Promoting awareness of Oesophageal Cancer. Scotland. OPA – Oesophageal Patients Association

4.4.3. Initial Response List

The raw data generated from the online questionnaire was downloaded unchanged onto a spreadsheet. Participants contact details were removed and stored confidentially for later use. Each participant was then given a unique identification number for audit purposes. Initial review identified clear immediate exclusions. These included duplicate uncertainties from the same responder (i.e. one responder asking exactly the same question twice), out of scope submissions and submissions too vague to generate a research question from. Individual respondents who asked two similar questions which could be categorised into one uncertainty had their responses

combined. This prevented over representation of a research uncertainty by a single responder. For example, “impact of lifestyle” and “impact of diet” asked by the same person would be combined to one uncertainty e.g. “impact of lifestyle factors including diet”. All remaining uncertainties were then allocated a broad umbrella category to help identify emerging themes during the formatting process.

4.4.4. Formatting and Verification of the Long List

Groups of similar or replicate responses were then rephrased into a single formatted uncertainty. The total number of original responses for each formatted uncertainty were logged. All long list uncertainties were then checked against the current evidence base to ensure they were true unknowns. True unknowns were defined as questions which could not be answered confidently by reliable systematic reviews or randomised controlled trials (RCTs). All related guidelines and review articles were identified from the Cochrane database, National Institute of Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), British Society of Gastroenterology (BSG) and British Medical Journal (BMJ). Other systematic reviews and studies, particularly RCT’s, were identified via an advanced PubMed Search.

The provisional long list was then reviewed by a professional subgroup of the steering committee. This included 2 BO experts from tertiary treatment centres (University College Hospital London and Salford Royal Foundation Trust), a Gastroenterology Research Nurse and Gastroenterology Research Registrar (both with a specialist interest in BO patient pathways). This verification process aimed to produce a concise but fairly represented long list of 30-40 questions to prevent over burdening participants and poor response rates during the interim prioritisation survey. This process did not involve the generation or prioritisation of research questions and therefore did not include a non-professional representative. The subgroup followed the process outlined in table 4.4.4-1 to reach a consensus agreement of the true uncertainties. This verification process aimed to produce a concise but fairly represented long list of 30-40 questions.

Table 4.4.4-1 Long List Review Process

1. Review of the linked literature to ensure each question is a true uncertainty 2. Consider unpublished RCTs which may influence or answer a defined uncertainty 3. Consider splitting or combining uncertainties to ensure a concise and fair representation of the initial responses. 4. Consider excluding uncertainties with very few initial responses and those with a significantly unbalanced professional to non-professional response rate. 5. Review the wording and length of each uncertainty to ensure lay person understanding.

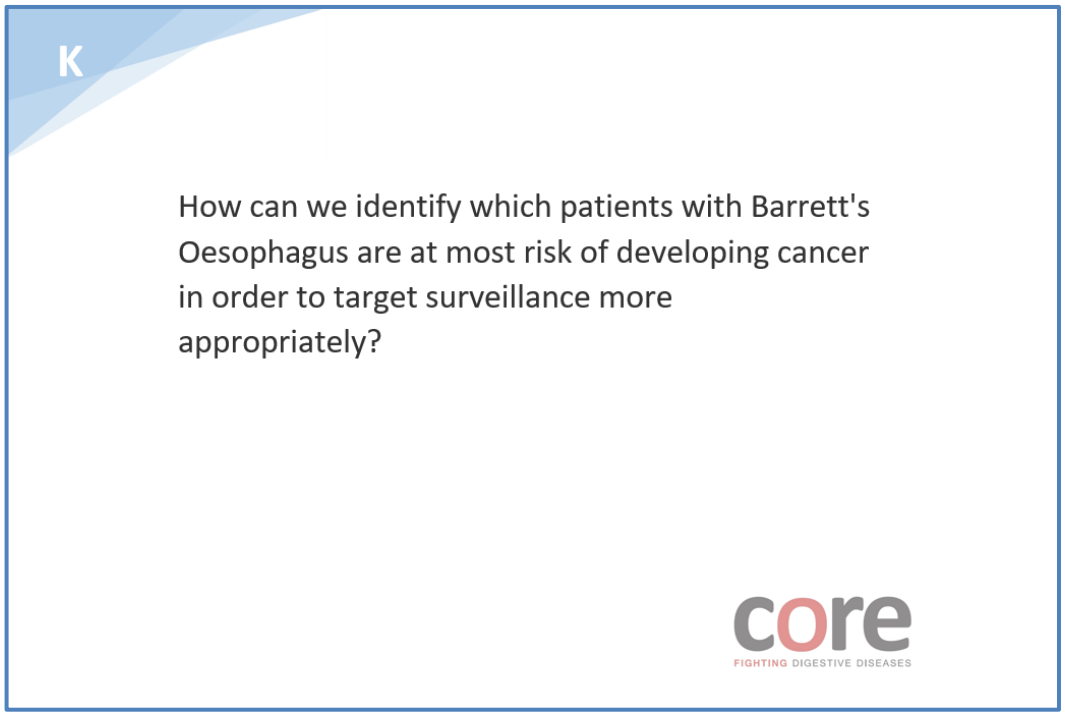
4.4.5. Interim Prioritisation Survey

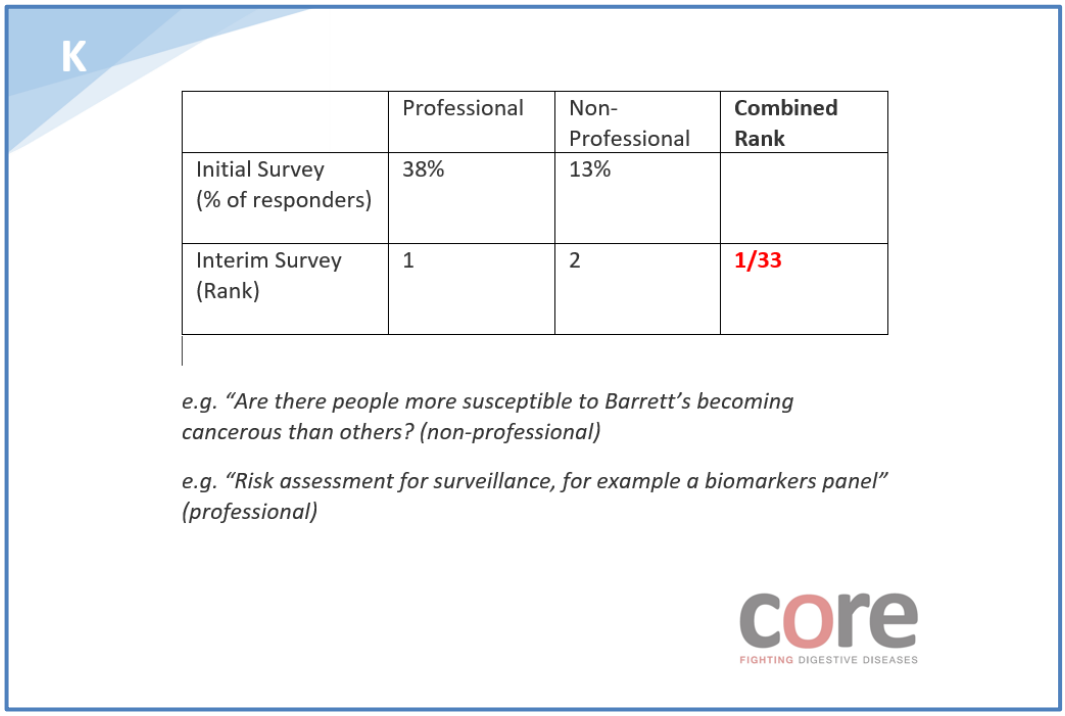
The first-round survey participants who left their contact details for future involvement were invited to take part in interim prioritisation. Participants were asked to complete an online survey which asked them to choose up to 10 questions from the long list and rank them in order of most importance (1= Most important, 10= Least important) (supplementary appendix 8.3.2). Professional and non-professional scores were initially kept separate. Total scores for each uncertainty were calculated using a reverse scoring system (e.g. rank 1=10 points and rank 10=1 point) before assigning a rank to each question. The professional and non-professional ranking scores were then combined to ensure an equally weighted overall rank.

4.4.6. Final "Top 10" Priority Setting Workshop

The final workshop allows parties to meet face to face to express their views, hear different perspectives and think more widely about the health problem (137). Key professional and non-professional parties, identified from the steering group, were invited to take part in the final prioritisation workshop. This was conducted via a modified Nominal Group Technique. This rigorous, yet flexible, format is a well-established approach to decision making (231). The workshop was led by a main co-ordinator and small team of neutral facilitators who assisted the process. In order to encourage less vocal members and prevent discussions been dominated by one or two strong characters the workshop was divided into small groups with balanced representation. Each participant within the groups reviewed the priorities and gave their view, this created open debate around each priority. This was followed by a shared ranking exercise conducted within each group. Groups were asked to encourage those less confident to share their experiences and thoughts. To assist in the ranking process, each group was provided with the priorities displayed on small cards. On the reverse of each card was more background information on how that uncertainty performed in the previous voting rounds (figure 4.4.6-1). This additional information can be helpful to participants, particularly patient representatives, when making a case for a specific uncertainty. However, we also stressed that the most "popular uncertainty" is not necessarily the right answer. Some research questions may be crucially important to a minority and hence warrant inclusion. Each subgroup agreed on their top 10 before all groups re-convened and compared the rankings. At this stage, individual group rankings were entered onto an excel spreadsheet to provide an aggregate ranked list. Any questions, comments or concerns were raised in a final whole group collective deliberation which honed in on the emerging top 10. Consensus, meaning unanimous agreement was achieved during this process without the need for decisions to be put to a majority vote.

Figure 4.4.6-1 Final Workshop Prompt Cards





4.5. Results

4.5.1. Initial Response List

The initial survey generated 629 uncertainties from 170 survey respondents, including 301 from non-professionals (n=90), 320 from professionals (n=80), and eight from the initial workshop. Details of the immediate clear exclusions are shown in table 4.5.1-1. The broad categories assigned to the remaining 522 uncertainties allowed greater familiarisation and distillation of the content. Recurring and similar uncertainties were combined to form an individual formatted research question. The distillation process was done by an analyst (JB, a gastroenterology specialist) and overseen by the University of Manchester academic adviser (JM). This process was then repeated for each broad category ultimately producing a provisional long list of 50 unique research questions.

Table 4.5.1-1 Initial "first pass" Uncertainty Exclusions

Reason for Exclusion	Number of Uncertainties
Out of Scope Uncertainties (Included responses not related to BO or GORD and responses too vague to generate a research question from)	77
Combined uncertainties (similar uncertainties proposed by the same responder were combined into 1 uncertainty)	27
Duplicate Uncertainties (the exact same uncertainty proposed by the same responder)	3
Total	107 (48 professional) (59 non-professional)

4.5.2. Formatting and Verification of the Long List

The provisional 50 uncertainties were then reviewed by a professional sub group of the steering committee. After review of the linked literature there was a consensus agreement to exclude 13 questions as not true uncertainties. 1 uncertainty was deemed to ask 2 separate questions and was therefore split. A further 5 uncertainties were considered to have significant crossover and consequently combined. This verification process produced a final long list of 33 unique questions ready for interim prioritisation.

4.5.3. Interim Priority Setting

Professional and non-professional scores for each question were calculated using the reverse scoring system described in the methodology. These scores were used to assign a rank. The combined ranks of both participant groups produced a prioritised long list which was reviewed

again by a sub group of the steering committee. The top 22/33 ranked uncertainties were taken forward to the final workshop (table 4.5.3-1). This number was chosen as there was a clear drop in scores beyond this uncertainty with agreement between both groups on their low priority status. No uncertainty lying outside the combined ranked top 20 fell inside the top 10 of either sub group. We also did not want to over load participants in the final workshop with an unmanageable number of questions to process and rank.

Table 4.5.3-1 Interim Prioritisation Long List Ranking

ID	Uncertainty	Professional Rank	Non-professional Rank	Combined Rank
K	How can we identify which patients with Barrett's Oesophagus are at most risk of developing cancer in order to target surveillance more appropriately?	1	2	1
P	How does the patient's genetic makeup and family history relate to their risk of disease progression (from Reflux - Barrett's Oesophagus - Precancerous - Cancer) and potential response to treatments?	7	9	2
O	When should we intervene with Barrett's Oesophagus; Is there a role for endoscopic intervention (ablation) of Barrett's Oesophagus with no precancerous changes?	9	7	2
Y	What are the most appropriate intervals for surveillance? And when can it be discontinued?	10	8	4
V	Which endoscopic therapy and techniques (RFA) are most effective, safest and economical when treating Barrett's Oesophagus with pre-cancer? Is there a role for other methods? (for example, cryoablation or argon plasma coagulation)	2	18	5
E	How effective are lifestyle interventions (diet, exercise, weight loss, smoking cessation) in improving reflux symptoms and can they alter individuals' risk of Barrett's Oesophagus or cancer?	16	5	6
M	Should Barrett's surveillance and new patient clinic be conducted by a dedicated service rather than all endoscopists? What impact would this have on patients, particularly pre-cancer diagnosis rates, patient education and satisfaction?	3	21	7
N	What key factors can be identified at a cellular level in the progression from a normal oesophagus - Barrett's Oesophagus - Precancerous - Cancer? Are these factors the same in younger patients or those post endoscopic treatment (ablation) for example?	22	3	8
S	Are there any long-term complications or risks with prolonged PPI use? Particularly their effects on bone density, salts in the blood (electrolytes), kidney function and cognitive impairment?	24	1	8
R	Are PPIs the only long-term answer for treating reflux? What other treatment options are available for patients who are intolerant, unresponsive or unwilling to take PPIs? (for example, surgery, minimally invasive techniques and newer medications)	21	4	8
T	What is the long-term effectiveness of endoscopic treatment for precancerous Barrett's or early cancers? Are response rates sustained? How does this effect the need for future endoscopic surveillance in these patients?	12	13	8
U	Is there any role for the newer, less invasive, techniques in controlling reflux? For example, electrical stimulation of the lower oesophagus from a device implanted underneath abdominal skin (endostim) or radiofrequency energy to the lower oesophageal muscle via endoscopy (stretta).	8	19	12
D	How can we raise the public awareness and profile of Acid Reflux and its links to Barrett's Oesophagus and Cancer?	18	10	13
Z	How can we accurately identify the high-risk people from the general population to target Barrett's Oesophagus screening?	5	24	14
X	Can Barrett' Oesophagus be reversed or its progression to cancer be halted by drug therapy (chemoprophylaxis)?	19	10	14
W	Is there a role for anti-reflux surgery to prevent Barrett 's with no precancerous changes progressing or to prevent disease recurrence after endoscopic treatment for pre-cancer or early cancer?	13	16	14
C	What key factors contribute to Gastroesophageal reflux? How significant is the presence of a hiatus hernia with regards to reflux severity, symptoms and cancer risk?	26	6	17
B	Is there a more acceptable, cost effective and accurate test for surveillance and screening of Barrett's Oesophagus in a primary care setting (GP's surgeries)?	4	30	18
J	How do we cope with the increasing demand for diagnostic and surveillance services? Is "blanket" surveillance of all Barrett's beneficial to patients or cost effective in its current model?	13	22	19
F	Are we able to distinguish between bile reflux and stomach acid reflux? What implications does this have on Barrett's Oesophagus development, cancer risk and treatments?	26	12	20
G	How does current surveillance practice across the UK compare to the current national guideline (British Society of Gastroenterology)? Would a national Barrett's Oesophagus Audit or Registry improve standards or care?	11	27	20
L	Is there a role for acetic acid or endoscopic image enhancers in routine Barrett's surveillance? What impact would this have on pre-cancer diagnosis, patient outcome and patient satisfaction.	6	32	20

Table 4.5.3-1 Interim Prioritisation Long List Ranking

Uncertainty	Professional Rank	Non-professional Rank	Combined Rank
Uncertainties excluded from the final workshop			
How does primary care (GP's, nurse practitioners and pharmacists) perceive Gastroesophageal Reflux and Barrett's Oesophagus? Does this have an impact on patients' health behaviour, endoscopy referrals or prescribing practices for example?	23	17	**23**
Is Barrett's Oesophagus over or under diagnosed at endoscopy? What training resources are there to help and improve our accuracy to prevent inappropriate surveillance and burden to patients?	15	26	24
What is the impact of Barrett's Oesophagus and its care pathways on patients' day to day quality of life?	17	24	24
Do patients with night time acid reflux have more severe disease and greater cancer risk. How can these symptoms be optimally treated?	30	15	26
How common is Barrett's Oesophagus in the general population and is it increasing in people of younger age?	33	13	27
How can we accurately identify and treat the less obvious, non-oesophageal, symptoms that can be caused by reflux? For example, a recurrent cough.	24	23	28
Are there any identifiable patient risk factors or triggers which are associated with breakthrough and treatment resistant symptoms?	20	28	29
How can the various associated charities and patient support groups work together more effectively?	29	20	30
Do environmental factors influence the number of people, from one region to another, diagnosed with Gastroesophageal reflux, Barrett's Oesophagus or Oesophageal Cancer?	26	31	31
Is there a role for using mobile phones and apps to create an interactive reflux or Barrett's Oesophagus network? Could these devices be used to support patients and also provide large amounts of research data more rapidly?	31	29	32
What is the role of pH testing (measuring acid reflux via a probe in the oesophagus) in Barrett's Oesophagus? What other parameters are available to measure reflux severity and impact?	32	33	33

4.5.4. Final "Top 10" Priority Setting Workshop

The final workshop of 13 participants included 5 Healthcare Professionals (3 Consultant Gastroenterologists and 2 Specialist Nurses) 8 patient representatives. Participants were divided into 3 small groups with fair professional and non-professional representation. Small group prioritising immediately revealed agreement on 5 uncertainties to include within the top 10. 3 of these uncertainties were unanimously agreed to form the top 3 ranking positions. After deliberation among all workshop participants, five uncertainties were deemed to overlap with others and were therefore combined (table 4.5.4-1), facilitating agreement on the remaining uncertainties to be included in the final top ten list. This discussion also allowed some important elements from low-ranked uncertainties to be pulled into the final top ten list. Such priorities might not have made the final selection on their own merit. For example, elements of the shortlisted priority, how the current surveillance practice across the UK compares to the current national guideline and would a national Barrett's oesophagus audit or registry improve standards or care, were combined with a more popular priority relating to the efficacy of a dedicated Barrett's oesophagus clinic. Secondary review of the excluded 7 uncertainties gave participants an opportunity to voice any final concerns or opinions. The uncertainty combinations and wording of

the final top 10 was subsequently checked to ensure adequate representation of the workshops discussions. Table 4.5.4-2 lists the final 10 research questions ranked in order of priority.

Table 4.5.4-1 Combined Uncertainties

Top 10 Research Priority Combinations		**Workshop Comments**
Should Barrett's surveillance and new patient clinic be conducted by a dedicated service rather than all endoscopists? What impact would this have on patients, particularly pre-cancer diagnosis rates, patient education and satisfaction?	How does current surveillance practice across the UK compare to the current national guideline (British Society of Gastroenterology)? Would a national Barrett's Oesophagus Audit or Registry improve standards or care?	Both these questions are targeting service and quality improvement. Research evaluating current standards of practice would need to be conducted in order to truly assess the impact of a dedicated Barrett's service, hence combined into one research question
What key factors can be identified at a cellular level in the progression from a normal oesophagus - Barrett's Oesophagus - Precancerous - Cancer? Are these factors the same in younger patients or those post endoscopic treatment (ablation) for example?	How does the patients' genetic makeup and family history relate to their risk of disease progression (from Reflux - Barrett's Oesophagus - Precancerous - Cancer) and potential response to treatments?	There was sufficient overlap to combine these questions while keeping the focus on translating research at a cellular/genetic level into real life gains for patients.
Are PPIs the only long-term answer for treating reflux? What other treatment options are available for patients who are intolerant, unresponsive or unwilling to take PPIs? (for example, surgery, minimally invasive techniques and newer medications)	Is there any role for the newer, less invasive, techniques in controlling reflux? For example, electrical stimulation of the lower oesophagus from a device implanted underneath abdominal skin (endostim) or radiofrequency energy to the lower oesophageal muscle via endoscopy (stretta).	Both these questions are asking about alternative treatments to PPI. Although this includes a range of treatments which will need a different research ventures, we thought they all shared a common goal and hence were combined to encompass all aspects in the top 10.
What are the most appropriate intervals for surveillance? And when can it be discontinued?	How do we cope with the increasing demand for diagnostic and surveillance services? Is "blanket" surveillance of all Barrett's beneficial to patients or cost effective in its current model?	Both these questions were deemed to question the appropriateness and efficacy of current surveillance and were therefore combined.
What is the long-term effectiveness of endoscopic treatment for precancerous Barrett's or early cancers? Are response rates sustained? How does this effect the need for future endoscopic surveillance in these patients?	Which endoscopic therapies and techniques (RFA) are most effective, safest and economical when treating Barrett's Oesophagus with pre-cancer? Is there a role for other methods? (for example, cryoablation or argon plasma coagulation)	Both these questions focus around the efficacy and durability of endoscopic therapy and were therefore combined.

Table 4.5.4-2 Final "Top 10" Research Priorities for Barrett's Oesophagus and Gastroesophageal Reflux Disease

Research Priority	ID	Final Rank
How can we accurately identify the high-risk people from the general population to target Barrett's Oesophagus screening?	Z	**1**
How can we achieve individual risk stratification of patients with Barrett's Oesophagus in order to target surveillance more appropriately?	K	**2**
Is there a more acceptable, cost effective and accurate test for surveillance and screening of Barrett's Oesophagus in a primary care setting?	B	**3**
Should Barrett's surveillance and new patient clinics be conducted by a dedicated service? How would this compare to current standards of practice in the UK and what impact would this have on patients? (for example, pre-cancer diagnosis rates, patient education, quality of life and satisfaction)	L+M	**4**
What is the long-term effectiveness of endoscopic treatment (radiofrequency ablation) for precancerous Barrett's oesophagus or early cancers? How does this affect the need for future endoscopic surveillance in these patients? Is there a role for other methods such as cryoablation or argon plasma coagulation in these care pathways?	T+V	**5**
Are there any long-term complications or risks with prolonged PPI use? Particularly their effects on bone density, salts in the blood (electrolytes), kidney function and cognitive impairment?	S	**6**
How does a patient's genetic makeup relate to their risk of disease progression at a cellular level (from Reflux - Barrett's Oesophagus - Precancerous - Cancer)? Particularly in younger patient groups, those with a strong family history or those with disease recurrence after endoscopic treatment (ablation)?	N+P	**7**
Are PPIs the only long term answer for treating reflux? What other treatment options are available for patients who are intolerant, unresponsive or unwilling to take PPIs? (e.g. surgery, newer medications or minimally invasive techniques such as endostim and stretta)	R+U	**8**
Is "blanket" surveillance of all Barrett's Oesophagus beneficial to patients or cost effective in its current model? Are current surveillance intervals appropriate and when can surveillance be safely discontinued?	Y+J	**9**
Is there a role for anti-reflux surgery to prevent Barrett 's with no precancerous changes progressing or to prevent disease recurrence after endoscopic treatment for pre-cancer?	W	**10**

Key;

- Consensus Agreement
- Patient centred
- Healthcare professional centred

4.6. Discussion

4.6.1. Findings

This exercise in research priority setting outlines ten key areas in which research efforts and resources should be focused. We think these priorities highlight crucial areas that can facilitate important long-term benefits to patients while equipping medical staff with knowledge, improved treatments, and enhanced services.

The incidence of gastroesophageal reflux disease and subsequent diagnoses of Barrett's oesophagus is increasing. Considering that most people with reflux do not have Barrett's oesophagus, this poses a huge problem for future health-care resources, an issue that is reflected strongly in our top ten list of uncertainties. An improved understanding of who to screen (first priority), coupled with an accurate and cost-effective primary care screening test (third priority) would obviate the need for invasive endoscopy in many patients. Not only might this be more acceptable to patients, but it would dramatically reduce some of the pressures in many endoscopy departments. The first and third priorities were originally ranked much lower in the interim priority-setting survey (combined ranks of 14 and 18, respectively), particularly by non-professionals. It is not uncommon for discrepancies to exist between the final workshop results and those of the interim survey. One of the roles of the final workshop is to highlight imbalances between professionals and non-professionals and to identify areas that might be important to a minority group or that might have been under-represented during the process. For example, the discrepancy seen here could reflect differences in the composition of the non-professional group that participated in the initial survey and that of the group involved in the interim survey. The latter group might have more direct experience with Barrett's oesophagus and relatively less vested interest in the gastroesophageal reflux disease population, the area to which these priorities relate. During the final workshop, all non-professional participants agreed on the importance of these issues after considering the wider implications to the population and initial survey responses.

There is currently insufficient evidence to provide conclusive individual risk stratification to all patients with Barrett's oesophagus (second and seventh priority) (232). Current risk stratification, in the UK, is based on BO length, the presence or absence of intestinal metaplasia and dysplasia. This allows decisions to be made regarding endoscopic therapy versus endoscopic surveillance (2-5 yearly) versus no surveillance (1). This algorithm leads to the majority of patients facing long term endoscopic surveillance. Data suggest that most patients with Barrett's oesophagus have low malignant potential and are perhaps more likely to die from other diseases than oesophageal adenocarcinoma (141-143,233). Thus, blanket surveillance might not be cost-effective or beneficial to most patients (ninth priority) (234). Without improved risk stratification models, this chronic

disease could impose an unnecessary burden on endoscopy provisions and on patients—this is clearly frustrating for both clinicians and patients and is echoed by several items in the top ten list. P53 is the only biomarker recommended for histopathological diagnosis of Barrett's oesophagus in a clinical setting (1), but the efficacy of this biomarker has been challenged in a recent consensus statement (2). To date, it has been very challenging to predict the progression of non-dysplastic Barrett's oesophagus using biomarkers, and there has been little success in translating research advances into routine clinical use (235). The mutational profile of Barrett's oesophagus appears highly heterogeneous, with mutations already occurring in non-dysplastic tissue. More recent developments in genomic sequencing are promising, and further research is clearly warranted (seventh priority) (236). Other research has focused on developing clinical risk scores. Sharma and colleagues conducted a longitudinal study of BO patients under surveillance between 1985 and 2014 with a median follow up of 5.9 years. They developed and validated a "progression in BO score" based on 4 risk factors (male sex, smoking, BO length, baseline LGD) for disease progression to HGD or OAC. This score categorises patients into low, intermediate or high risk groups reflecting their annual risk of progression to HGD or OAC (Low 0.12%, Intermediate 0.73%, High 2.1%) (237,238). We expect that a clinical and biochemical profile together will provide enhanced individual risk stratification reshaping surveillance practices with improved identification and treatment of patients at high risk while safely relaxing follow-up intervals or even discontinuing surveillance for others.

Advances in screening and risk stratification may take years to fully develop before they translate to standard care. Some uncertainties therefore focused on an immediate need to improve service delivery and quality (fourth priority). An assessment of the effect of a dedicated service for patients with Barrett's oesophagus (endoscopy surveillance and Barrett's clinic) should provide some insight into the efficacy and acceptability of existing treatment delivery pathways. Some historical evidence (144) and findings presented in this thesis (chapter 2) suggests that patients with Barrett's oesophagus have often received haphazard and inconsistent follow-up care. The design and implementation of a dedicated service must consider the patient's perspective, and its success should be measured using both clinical outcomes (e.g. diagnosis ratification, endoscopy quality and dysplasia diagnosis rates) and patient-centred outcomes (e.g. patient education, HRQOL and satisfaction with services). A randomised intervention study to assess the suitability and efficacy of a dedicated service compared with current practice would provide valuable insight and could help to shape future health-care delivery for patients with this disease. We envisage the establishment of dedicated surveillance endoscopy services and new patient clinics managed by trained nurse endoscopists alongside a consultant gastroenterologist with an interest in Barrett's oesophagus and oesophageal adenocarcinoma.

Some uncertainties might be oriented specifically towards either patients or professionals. One particular area that received consistent patient interest was safe and effective treatment of acid reflux (sixth and eighth priorities). Many patients with gastro-oesophageal reflux disease and most patients with Barrett's oesophagus need long-term treatment with proton-pump inhibitors (PPIs), sometimes for decades. Patients are rightly concerned about long-term drug safety, which has been questioned on the basis of findings from observational studies (239). Although no causality can be proven in these studies, long-term drug safety is an important area that needs further clarity, particularly in view of the vast unmonitored use of these drugs. This uncertainty seems to have been overlooked or possibly dismissed by professionals on the basis of limitations of epidemiological and observational studies. To address this crucially important patient question, future studies should be more specific and definitive in focus and prospective in design (240). For example, Jo and colleagues (184) prospectively examined the effect of PPI use on parameters of bone health. The results of this small randomised controlled trial showed that 8 weeks of PPI therapy might directly alter bone metabolism, particularly in people older than 60 years.

Substantial proportions of patients are intolerant, poorly responsive, or unwilling to take PPIs; this issue was also deemed crucially important to the non-professionals involved in this process. Such patients can be difficult to treat since there are few adequately developed or widely available alternatives to PPIs. This issue was echoed in the top ten list by an interest in newer, minimally invasive, or surgical non-drug treatments (eighth priority) and perhaps reflects a need for a low-risk, long-term treatment strategy and concerns associated with lifelong oral medication. Some minimally invasive surgical and endoscopic anti-reflux techniques have shown promise. However, many of these trials were small and uncontrolled, with no clear standardised methods of assessing subjective or objective endpoints. Stretta—radiofrequency energy delivered to the lower oesophageal muscle via endoscopy—has been used for 15 years, yet conflicting reports regarding its efficacy still exist (241-244). Perhaps increased focus should now be put on new, promising techniques including magnetic sphincter augmentation (245), Endostim (246-248), and transoral incisionless fundoplication (249,250). Assessment of the efficacy and durability of these approaches will necessitate large, multicentre, randomised studies (fifth and tenth priorities). Researchers must also consider a standardised approach for assessing primary and secondary outcomes to draw clear between-study comparisons and more definitive conclusions.

Advances in radiofrequency ablation technologies and regimens have led to substantial improvements in the safety and efficacy of treatment for dysplastic Barrett's oesophagus. This is reflected by durability data from the Halo registry (251). However, a small group of patients have disease recurrence (101). Long-term surveillance after endoscopic therapy is therefore imperative. To develop optimal surveillance strategies, we need long-term durability studies

coupled with a better appreciation of disease recurrence at a cellular level (fifth and seventh priorities).

Although radiofrequency ablation, particularly circumferential treatments, have become the mainstay of therapy for flat dysplastic Barrett's oesophagus, some controversy around the most effective methods for treating focal disease (252) and the potential roles of adjunctive treatments remains (e.g. argon plasma coagulation and cryotherapy) (253,254).

Within the excluded uncertainties, three were perhaps surprising. The first related to the use of radiofrequency ablation to treat non-dysplastic Barrett's oesophagus, which is common in other health-care settings, particularly the private health-care system in the USA (255). Although this topic ranked highly during interim prioritisation, participants of the final workshop thought further research to investigate this treatment pathway was impractical and too expensive within a publicly funded NHS. Sufficient evidence argues against this practice when one considers non-dysplastic cancer conversion rates, procedural complications, and cost-effectiveness. Second, the role of chemoprophylaxis was highly rated in earlier rounds of prioritisation, and its ultimate exclusion might have been due to the imminent conclusion of the AspECT trial (256,257), a phase 3 randomised trial of aspirin and esomeprazole chemoprevention in Barrett's oesophagus that will provide some answers to this unknown. Third, the effect of lifestyle on gastroesophageal reflux symptoms and progression of Barrett's oesophagus was popular among patient participants during early prioritisation rounds but fell out of favour in the final workshop. One explanation for this might be the difficulty this research question poses in terms of trial design, outcome measures, and the long length of follow-up needed to generate reliable results.

4.6.2. Strength and Validity of Methods

Throughout this process, we tried to engage a diverse, representative group to ensure the democratic legitimacy of the results. Final workshop participants were chosen on the basis of a high level of previous expertise and experience to provide a contributory role. Some people might argue that this group is therefore exclusive and not truly representative of the broader interested parties. However, participants, particularly non-professionals, were empowered to speak on behalf of all patients by supplying them with a wide selection of population data from the previous rounds of voting. This allowed participants to reflect not only on their individual experiences but also the views of the wider patient population (124,139).

4.6.3. Limitations

A lack of current evidence in some research areas may reflect a particularly difficult research endpoint to achieve or a lack in translation from laboratory advances into real life gains for patients.

Previous priority-setting partnerships that used the same methodologies have been criticised for generating loosely defined questions that are difficult to transform into actual research proposals (258). We have therefore attempted to formulate detailed, well defined uncertainties that still reflect the original scope of responses.

The methodologies are somewhat selective by nature. First, the survey was done in the English language and was primarily internet-based with no means of calculating response rates (259). Second, many respondents, particularly those associated with charities, are likely to be white, middle class, and with a high background educational level. By comparison, individuals who are harder to reach, such as people in low socioeconomic groups and vulnerable patients, might have the greatest unmet needs and stand the most to gain (258). However, engaging the disengaged is extremely challenging, especially with finite financial resources and manpower. Third, to distil the original verbatim responses into a representative shortlist, a degree of interpretation must occur. Ideas or information might have been lost or misunderstood during this process.

Our study has a smaller sample size than some studies using James Lind Alliance techniques, especially in view of the prevalence of Barrett's oesophagus and gastro-oesophageal reflux disease. This limitation was counteracted by asking respondents to choose up to five initial uncertainties. The subsequent qualitative elements within the methodologies ensures that the success of the project does not rely purely on a majority vote. Clear thematic saturation of research uncertainties was achieved during the initial survey, allowing progression through the ranking stages. Considered deliberation in the final workshop also allowed for the inclusion of priorities originally generated by minority groups. Finally, Barrett's oesophagus and gastro-oesophageal reflux disease are diseases that affect people everywhere and are particularly prevalent in the developed world. This study is representative of patients and front-line staff in the UK's NHS, and other countries with different health-care provisions might produce different priorities.

4.6.4. Dissemination and Potential Impact

Effective dissemination of these research priorities to the appropriate audience is essential for the success of this project. This initiative is the first to tackle this important issue in Barrett's oesophagus and gastro-oesophageal reflux disease, and we hope that it will be taken into consideration by researchers and potential funders, such as the National Institute for Health Research, the Association for Medical Charities, and the Medical Research Council. Further dissemination via conference presentation and communication of the results via CORE will be essential.

The immediate effects of these results are of interest and can be assessed in terms of the number of research projects undertaken, developed, or funded within the next 1–2 years. Assessing the long-term and broader population benefits of this work will be much more difficult. Previous priority-setting partnerships have been successful for several reasons. Some have highlighted areas previously overlooked or not considered. For example the impact of exercise on asthmatics and the treatment of perianal crohns disease were both included in their respective top 10's (140,259). Others have substantially influenced the immediate direction of research; most notably, the priority-setting partnership for urinary incontinence helped attract funding and research developments in six of ten priorities within 12 months.7 (139)

Since completing this research priority setting exercise we have disseminated the results via the following modes;

1) Publicised via the BSG's charity CORE (now Guts UK) website and other associated charities such as Action Against Heartburn.
2) Invited for an oral and poster presentation at the CRUK International Oesophageal Cancer Symposium (Cancer research UK Cambridge Institute 27th-28th April 2017). This symposium brings together experts and researchers across the whole realm of Oesophageal cancer. This meeting has also developed strong links with experienced patient representatives
3) Free access publication with The Lancet (Gastroenterology and Hepatology).
4) Social Media dissemination via the following twitter accounts; BSG (5,157 followers), CORE (1005 followers), The Lancet Gastroenterology and Hepatology (2,175 followers), figure 4.6.4-1.

Figure 4.6.4-1 Social Media Dissemination.

5) Olympus and Guts UK fellowship. On the back of this work, Guts UK and Olympus offered a 3-year registrar PhD fellowship for endoscopy research on Barrett's Oesophagus and Gastroesophageal Reflux Disease (GORD). The total value of the grant was £210,000. "The

research project will need to address one or more of the Top 10 research priorities in Barrett's Oesophagus and gastroesophageal reflux disease.

4.7. Conclusions

This top 10 list of research uncertainties has been generated by a recognised, robust and transparent process. The advent of patient and public involvement in both research and health-care improvement is undoubtedly essential. The identification of research priorities is perhaps where their greatest effect can be achieved. This top ten list of patient-centred research questions is the first for Barrett's oesophagus and gastro-oesophageal reflux disease. We hope these priorities will help focus researchers' efforts and influence future funding of areas in which meaningful gains can be made for patients. In view of the prevalence of Barrett's oesophagus and gastro-oesophageal reflux disease, this priority list has the potential to affect many patients and health-care providers. As the research advances, this process should be repeated to maintain a relevant and up-to-date focus for researchers.

5. Chapter 5 - Dedicated service improves the accuracy of Barrett's oesophagus surveillance: a prospective comparative cohort study

5.1. Introduction

The incidence of oesophageal adenocarcinoma (OAC) in the western world is increasing (151,188). Once invasive this cancer harbours a poor prognosis (3,153) and limited treatment options. Since the mid 1980's Barrett's oesophagus has been firmly recognised as a pre-cursor to OAC (260-262). The European general population prevalence of BO has been reported at 1.6% and 1.3% (4,5) with an annual cancer conversion rate of 0.33% in a recent meta-analysis (6). Over the last 30 years there have been significant research gains in the attempt to diminish the progression of BO to OAC. In particular, retrospective cohort and comparative studies suggest that endoscopic surveillance correlates with earlier staging and improved cancer survivorship (9-15). This has culminated into the development of national surveillance guidelines and dysplasia treatment pathways in Europe and the US (1,2,16,263).

Although endoscopic surveillance is widely practiced it remains a controversial topic with no published randomised controlled trials supporting its efficacy (17), and therefore uncertainty remains about best practice. Indeed, this area was ranked number 4 in the top 10 research priorities for future BO and gastroesophageal reflux disease (GORD) research in a recent UK-wide exercise which engaged both patients and healthcare providers (264). The latest British Society of Gastroenterology (BSG) guidelines provided clearer diagnostic criteria, defined surveillance intervals and a minimum endoscopic dataset for reporting (1). In the absence of conclusive evidence for the use of advanced imaging modalities, they also advocate high definition white light endoscopy with Seattle biopsy protocol (65). Pre-guideline UK data suggest BO patients have received inconsistent care from perhaps less well informed or disengaged physicians (144).

5.1.1. Aims

The aim of this study was to define current care in the post guideline era, and to judge whether a dedicated BO list performs better in terms of BSG guidance metrics and compliance than a non-dedicated list in a typical NHS hospital setting.

5.1.2. Ethical Considerations

This piece of work incorporated elements both of service evaluation and clinical audit defined by the NHS Health Research Authority (191), therefore formal ethical approval was not required.

5.2. Methods

All patients due BO surveillance between January 2016 and July 2017 at a single NHS district general hospital in the UK were included in the cohort for analysis. The majority of patients enrolled in surveillance were identified prospectively via the endoscopy booking department or at endoscopy. Patients underwent their surveillance endoscopy on a dedicated BO list or a non-dedicated endoscopy list. This routing process was not randomised or influenced by the study team and occurred purely due to endoscopy capacity and patient availability on dates they were offered their test. We prospectively collected data against the BSG dataset for endoscopy reporting (table 5.2-1) whilst also recording the number of biopsies taken, histology results and appropriateness of surveillance intervals. Prospective surveillance data were then compared to each patient's previous surveillance endoscopy. Data are expressed as mean +/- SD and percentiles unless otherwise stated. Fisher's exact test was used for comparison of means. A p value of <0.05 was taken to show statistical significance. All data were collected by JB (clinical research fellow in gastroenterology) and TR (Core Medical Trainee). Subsequent analysis was conducted by KC (Gastroenterology Specialist Trainee) and JB.

Table 5.2-1 Minimum endoscopic dataset required when reporting Barrett's oesophagus

Finding	**Reporting System**	**Nomenclature**
Barrett's oesophagus length	Prague Classification	CnMn (where n is length in cm)
Barrett's islands	Describe distance from the incisors and length in cm	Descriptive in the text
Hiatus hernia	Distance between DP and GOJ	Yes/no; cm
Visible lesions	Number and distance from incisors	Yes/no; cm
Classification of visible lesions	Paris Classification	0-1p, protruded pedunculated 0-1s, protruded sessile 0-IIa, superficial elevated 0-IIb, flat 0-IIc, superficial depressed 0-III excavated
Biopsies	Location and number of samples	N cm (distance from incisors) Xn

GOJ, gastro-oesophageal junction. DP, diaphragmatic pinch. (1)

5.3. Results

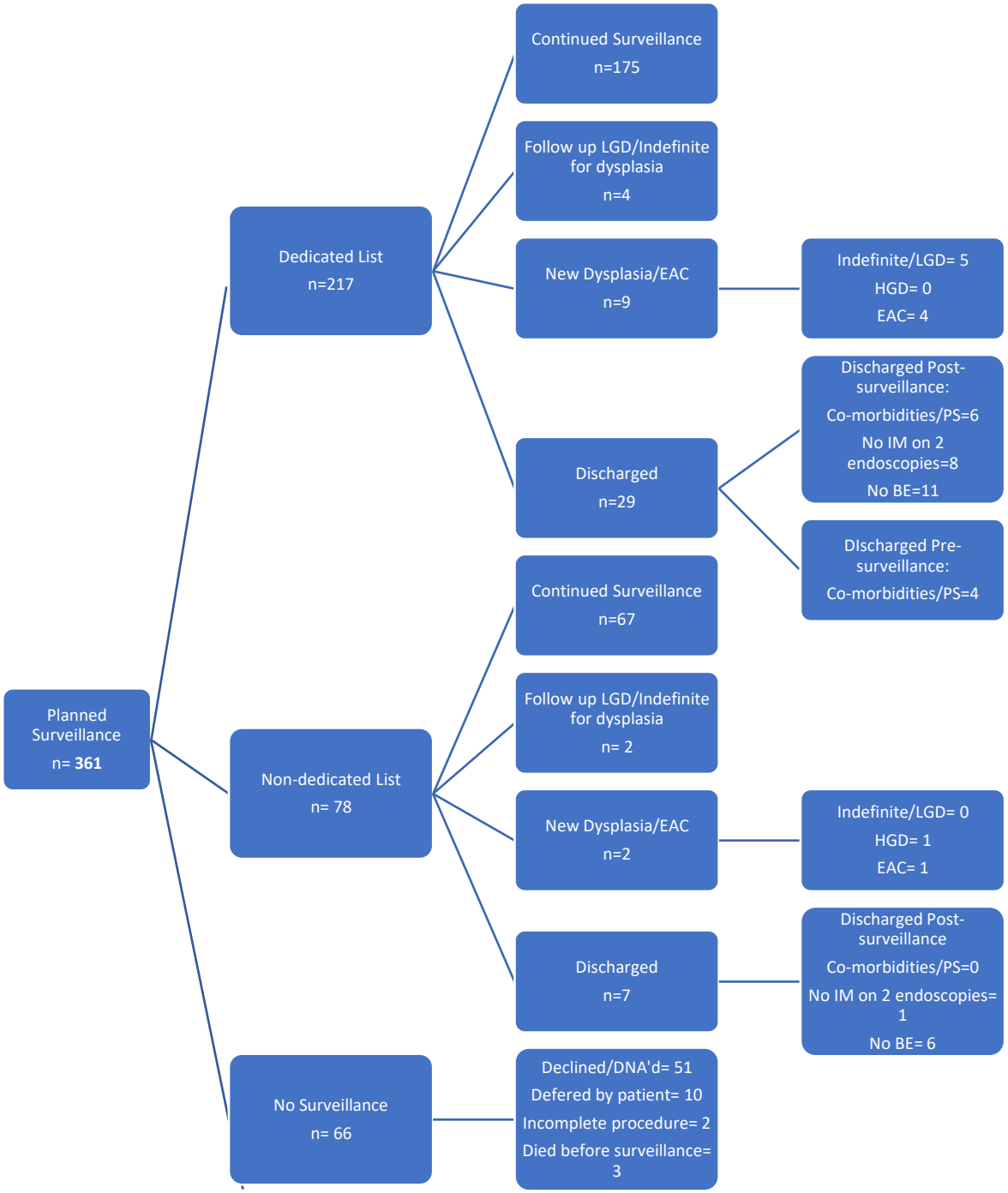
5.3.1. Patient Groups and Demographics

361 patients were scheduled for BO surveillance between January 2016 and July 2017. Of these, 217 attended a dedicated BO list, 78 a generic service list and 66 did not have their endoscopy completed (figure 5.3.1-1). Both surveillance groups had comparable demographics in terms of age, sex, Prague classification and co-morbidity prevalence (table 5.3.1-1)

Table 5.3.1-1 Cohort Demographics

Demographics		**Dedicated List (N=188)**	**Non-dedicated List (N=71)**
Age (yrs. mean +/- SD)		64 (+/- 9.6)	66 (+/- 9.2)
Co-morbidities	0	91 (48.4%)	28 (39.4%)
	1	48 (25.5%)	28 (25.0%)
	>=2	49 (26.1%)	25 (35.4%)
Sex	M	132 (70.2%)	53 (74.6%)
	F	56 (29.8%)	18 (25.4%)
Average Prague criteria		C2.2 M3.6	C2.5 M4.1

Figure 5.3.1-1 Barrett's Oesophagus Surveillance January 2016 – July 2017



BO, Barrett's oesophagus. LGD, low grade dysplasia. HGD, high grade dysplasia. OAC, oesophageal adenocarcinoma. PS, performance status. IM, intestinal metaplasia

5.3.2. Endoscopists

The dedicated list was conducted by a single endoscopist with a specialist interest in BO. By comparison, patients attending the non-dedicated lists (n=78) and retrospective lists (n=229) had their endoscopy undertaken by a range of general endoscopists. Nurse endoscopists (39%) and consultant gastroenterologists (37%) conducted the most procedures followed by speciality trainees (13%) and consultant surgeons (11%). In total there were 20 (prospective) and 35 (retrospective) individual health care professionals providing surveillance for these non-dedicated cohorts respectively with an average of 2.3 and 4.1 surveillance procedures per endoscopist per year.

5.3.3. Endoscopy Reporting

Patients who were discharged from surveillance were excluded from the 2 cohorts prior to analysis of the endoscopy reporting (dedicated list n=188, non-dedicated list n=71, total n=259). In addition, the previous endoscopy reports of the 259 were retrospectively reviewed to provide a historic comparison of service provision. Of the 259 retrospective reports, 14 were excluded as their prior endoscopy pre dated BSG guideline publication and a further 16 were excluded as their report were unavailable.

The dedicated BO endoscopy list achieved greater adherence to the BSG guideline for BO endoscopy reporting when compared to both the non-dedicated and retrospective cohorts (table 5.3.3-1). In particular; Prague classification (100% vs 87.3% P<0.0001), Barrett's island description (96.6% vs 0% p<0.0001), hiatus hernia delineation (100% vs 64.8% p<0.0001), visible lesion documentation (100% vs 94.4% p=0.0053), visible lesion description (94.4% vs 0%, P<0.0001) and number and location of biopsies taken (99.5% vs 5.6% p<0.0001). The prevalence of visible lesions documented was comparable between the cohorts however there were significantly more Barrett's islands reported on the dedicated list. This likely reflects the enhanced reporting seen in the dedicated cohort than an actual difference in cohort prevalence.

Table 5.3.3-1 Endoscopy Reporting and Quality Indicators

Standards	**Dedicated BO surveillance endoscopy, n= 188** **January 2016-July 2017**	**Non-dedicated surveillance endoscopy, n= 71** **January 2016-July 2017**	**p value** **(Dedicated vs Non-dedicated)**	**Retrospective previous BO surveillance, n= 229** **November 2013-June 2016**	**p value** **Dedicated vs Retrospective**
BO length (Prague CnMn)	100% (n=188)	87.3% (n=62)	p<0.0001	82.5% (n=189)	p<0.0001
BO island description (Distance from incisors and length)	96.6% (n=28)	0% (n=0)	p<0.0001	17.6% (n=3)	p<0.0001
BO island prevalence	15.4% (n=29)	5.6% (n= 4)	p=0.02	7.4% (n=17)	p=0.0074
Hiatus hernia documentation	100% (n=188)	64.8% (n=46)	p<0.0001	63.3% (n=145)	p<0.0001
Visible lesion documentation (yes or no)	100% (n=188)	94.4% (n=67)	p=0.005	89.9% (n=206)	p<0.0001
Visible lesion prevalence	9.6% (n=18)	8.5% (n=6)	p=0.50	4.8% (n=11)	p=0.0436
Visible lesion description (distance from incisors + Paris classification)	94.4% (n=17)	0% (n=0)	p<0.0001	0% (n=0)	p<0.0001
Biopsies (location and number taken)	99.5% (n=187)	5.6% (n=4)	p<0.0001	6.9% (n=16)	p<0.0001

GOJ, gastro-oesophageal junction. DP, diaphragmatic pinch.

* Not applicable; during this timeframe endoscopists referred to the dedicated BO service to arrange

5.3.4. Other quality indicators

Adherence to Seattle protocol was significantly greater in the dedicated cohort when calculated on a case by case basis (table 5.3.4-1). However, this did not translate into significantly higher rates of intestinal metaplasia (table 5.3.4-1) or dysplasia (table 5.3.4-2) (this calculation excluded patients with a prior diagnosis of dysplasia). Overall discharge rates were also unaffected by the type of list employed (table 5.3.4-2). Interestingly, it appears that more patients were discharged from the dedicated list due to co-morbidities or performance status (n=10, 34.5% of discharges) compared to none in the non-dedicated list. Patients in the non-dedicated cohort (n=78) were more likely to be discharged (n=7) from a consultant led list (n= 6/7) than a nurse led list (n= 0/7) despite conducting a comparable number of procedures (30 consultant led and 31 nurse led). Within the same timeframe 197 new BO diagnoses were referred to the service for consideration of surveillance. After further assessment, a large proportion of these (n= 60, 30.5%) were not enrolled into surveillance (the reasons are documented in table 5.3.4-2).

Table 5.3.4-1 Other endoscopy quality indicators

Standards	**Dedicated BO surveillance endoscopy, n= 188** **January 2016-July 2017**	**Non-dedicated surveillance endoscopy, n= 71** **January 2016-July 2017**	**p value** **(Dedicated vs Non-dedicated)**	**Retrospective previous BO surveillance, n= 229** **November 2013-June 2016**	**p value** **Dedicated vs Retrospective**
Average number of biopsies (histology reported)	7.5	6.0		6.3	
Average Prague (M)	3.6	4.1		4.1	
Seattle Protocol adherence % (case by case †)	72% (n=135/188)	42% (n=26/62)	p<0.0001	50% (n=94/189)	p<0.0001
Intestinal metaplasia	79.8% (n= 150)	73.1% (n= 51)	p=0.12	79.9% (n=183)	p=0.532
Surveillance interval appropriate	100% (n=188)	Na ‡		75% (n=147)	p<0.0001

† Expected Seattle biopsy number (Prague M / 2x4) vs Number of biopsies taken

‡ Not applicable; during this timeframe endoscopists referred to the dedicated BO service to arrange.

Table 5.3.4-2: Dysplasia diagnoses and discharge rates (January 2016 – July 2017)

	Dedicated BO surveillance endoscopy **N= 217 †**	**Non-dedicated surveillance endoscopy** **N= 78 †**	**p value**
New dysplasia diagnoses			
Indefinite/LGD	5	0	
HGD	0	1	
OAC	4	1	
Total	9	2	
Diagnosis Rate ‡	4.3%	2.6%	p=0.41
Discharges from surveillance			
Discharged Pre- endoscopy	4 (Co-morbidities/PS)	0	
Discharged Post- endoscopy	Co-morbidities/PS= 6 No IM on 2 endoscopies= 8 No BO= 11	Co-morbidities/PS= 0 No IM on 2 endoscopies= 1 No BO= 6	
Total Discharged	29	7	
Total Discharge Rate %	13.4%	9.0%	p=0.21
Discharges of new referrals			
New Diagnoses Referred	197		
Enrolled in surveillance	137		
Discharged for no surveillance	60 (Co-morbidities/PS= 23) (No IM on 2 endoscopies= 28) (No BO on re-assessment= 9)		
New diagnosis discharge rate	30.5%		

LGD, low grade dysplasia. HGD, high grade dysplasia. OAC, oesophageal adenocarcinoma. PS, performance status. IM, intestinal metaplasia. BO, Barrett's oesophagus.

† These numbers include those who were discharged after their endoscopy

‡ This calculation excludes LGD and indefinite for dysplasia follow up patients (n=4 for dedicated list, n=2 for non-dedicated list) and patients discharged pre-endoscopy (n=4 for dedicated list).

5.4. Discussion

This mixed prospective and retrospective cohort study demonstrates some potential benefits of a dedicated BO service and provides an insight into current BO surveillance practices in the NHS. The major finding from this study was the enhanced adherence to current standards of care achieved by the implementation of a dedicated BO service list, rather than unmanaged allocation of BO patients to any clinician undertaking endoscopy in mixed, unselected lists. In particular, improved endoscopic reporting in terms of BO delineation: Prague classification, hiatus hernia and island descriptions. Adherence to surveillance intervals was also improved when compared to the retrospective data collected. This would potentially prevent over-surveillance in many cases as the majority of patients with inappropriate surveillance intervals had short segment disease with a 2-year interval (88%, n=42/48). The dedicated service also discharged 13.4% of patients from surveillance, in particular patients with significant co-morbidities or poor performance status. These discharge rates are comparable to historic UK data from a specialist centre (11%) (145). These findings probably reflect a vested interest of the BO service provider when compared to a general endoscopist who is often just the "technician" of surveillance, probably unaware of the detailed guidance. This is echoed by the lack of discharges, seen in this study, by nurse endoscopists, which is an important consideration when planning future surveillance care pathways that may be nurse led. The dedicated service also used a BO clinic as a platform to have more informed discussions about surveillance appropriateness. This is useful when one considers the number of patients enrolled at a time when diagnostic criteria were less clear (265). The main use of the BO clinic however was for consultation of newly diagnosed patients. This clinic provided an opportunity to ratify the diagnosis and assess the appropriateness of surveillance in terms of patient fitness and willingness. This service appears most valuable as a high proportion (n=60, 30.5%) of patients may have been inappropriately or automatically enrolled in longer term surveillance without review. This could cause undue patient burden and impact on endoscopy provisions. It is unclear from this study what proportion of this assessment and decision making would have happened without the service in place.

Although not found to be statistically significant this study suggests that a dedicated BO surveillance list may diagnose dysplasia more readily than those attending other "ad hoc" lists during the same time frame (4.3% vs 2.6%). There are a number of potential reasons for this. Firstly, limiting the number of endoscopists conducting surveillance may allow them to become more experienced and proficient in identifying and sampling abnormal areas. This is supported by a recent study which found a dramatic increase in dysplasia detection on a dedicated list (8-18%) (266). However, this study was part retrospective in design comparing data from endoscopies conducted as far back as

2007. This data may also reflect a tertiary setting patient population with a higher concentrate of at-risk BO patients. Secondly, the dedicated BO service was also limited to 7 gastroscopies per session. Current recommendations from the Joint advisory group on GI endoscopy is a maximum of 210 minutes per endoscopy list which crudely equates to 10 gastroscopies or 5 colonoscopies per list (267). This adjusted allotted time for surveillance procedures ensures adequate time for mucosal inspection and Seattle biopsies, particularly in long segment disease. Although oesophageal withdrawal time was not documented, previous research suggests a Barrett's inspection time of greater than 1 minute per centimetre detects more endoscopically suspicious lesions (54.2% vs 13.3%, p = 0.04) and higher rates of HGD and OAC (40.2% vs 6.7%, p = 0.06) (268). This is now reflected in the most recent publication of Quality Standards in upper gastrointestinal endoscopy (269). However, further clarification is needed as this recommendation is based on a post hoc analysis of a single clinical trial. Finally, the dedicated list achieved significantly greater compliance to the Seattle protocol. Logically, one would expect low adherence to biopsy protocols to be associated with lower dysplasia detection rates. This finding was demonstrated in a large US cohort of community based BO surveillance where overall adherence was reported at 51.2% (270). In contrast, one would also expect a greater number of biopsies to yield significantly higher rates of IM (271), which was not demonstrated in this study. A larger sample size would be needed to confidently delineate whether there is a significant difference in IM and dysplasia rates between these groups.

5.5. Limitations

One must be cautious when interpreting and generalising the findings of this study due to the following limitations. Firstly, the mixed prospective and retrospective design, small sample size, from a single centre and over a short time frame may introduce significant bias. Secondly, this non-randomised study, was also an assessment against a single guideline (BSG), there are a number of other quality standards of upper GI endoscopy that have gone unmeasured; for example, inspection times, adequacy of mucosal visualisation, patient discomfort scores and sedation rates (269). Thirdly, there are other potential confounding patient factors which may influence dysplasia diagnosis rates between groups. These include smoking status, family history of BO or OAC, PPI usage and waist to hip ratio (232). However, despite these limitations, the findings appear both consistent with the literature, and show that standards can be met if the clinical service manages its patients proactively.

5.6. Conclusion

The right patient undergoing the right test at the right time is a mantra which applies to all surveillance strategies. This study demonstrates a dedicated service can ratify the cohort of

surveyed patients (right patient), conduct a more consistent test in line with current best practice (right test) and ensure appropriate surveillance intervals (right time). In time, a dedicated service may provide a more stable transition to future guidelines for example easier adaptation to individual risk stratification models and advanced endoscopic techniques. From this single centre study, it remains unclear whether such a service can consistently improve clinical outcomes such as dysplasia diagnosis rates. Further prospective, higher powered, multicentre studies are needed to evaluate these potential clinical gains alongside patient centred outcomes such as health related quality of life, disease specific knowledge, and overall satisfaction with services (156).

6. Chapter 6 – Discussion

6.1. Barrett's oesophagus patient burden

Generally speaking quantitative measurement of HRQOL offers an important insight into the prevalence of disease impacts within a defined population. For the same reason it can be helpful when implementing or comparing care pathways. Further assessments can also be made between diseases which help raise awareness outside of the defined field. Relating issues to a wider audience may also provoke researchers and clinicians to learn from other care models. This thesis provides both a quantitative and qualitative account of the patient's perspective of BO. Symptom control, burden of surveillance endoscopy, worry of oesophageal cancer and disease specific knowledge are central to patients' experiences. These factors should be considered when developing future care pathways, clinical trials or a BO specific PROM.

There are four major difficulties with BO HRQOL measurement which future researchers must be mindful of. Firstly, quantitative HRQOL measurement only captures a point in time. A single measurement is more open to the influence of confounding factors, some of which will be unmeasurable and may vary over time. Questionnaire recall periods attempt to address this however they are not all consistent, often short or undefined. To counteract this one could re-test a subset of the cohort to assess for consistency over time. Secondly, researchers must consider the significant impact of confounding factors, such as co morbid disease, before drawing conclusions regarding the impact of the disease in question. The quantitative study (chapter 3) showed significant differences reverted after controlling for confounders with propensity score matching. Thirdly, quantitative HRQOL measurement can look for associations between measures, for example symptom severity and levels of anxiety. It is important to remember that such findings are associations with no firm causality which is often not the case in HRQOL literature. The complexity of these interactions cannot be fully deciphered by quantitative methodology alone. The research conducted in this thesis demonstrates the value of a concurrent or nested in-depth qualitative study. For example, chapter 3 demonstrated BO patients generally had good reflux symptom control and statistically better than GORD patients, a finding supported by prior research. Further sub analysis showed those BO patients with worse reflux symptoms had significantly higher levels of oesophageal cancer specific worry. The qualitative study adds a greater understanding to these findings. Once again interview participants reported good background symptom control, as per the quantitative findings, but can also suffer from unpredictable symptoms flares, a finding which would not be captured in a one-off questionnaire. Furthermore, the qualitative analysis discovered that poor symptom control may lead to worries and concerns regarding cancer rather than the opposing direction. This finding may also in part explain why the GORD cohort had

surprisingly high levels of cancer specific worry. Fourthly, a lack of a validated and specific BO PROM. The use of multiple instruments to capture possible impacts is cumbersome for participants and researchers. This approach creates a lengthy questionnaire which may reduce response rates and raises concerns regarding the effects of questionnaire ordering (208). Choice of instruments is also left to the discretion of the researcher who may have limited HRQOL research background and conducting a study where HRQOL is a secondary or tertiary outcome measure. A tokenistic approach to HRQOL measurement may lead to the omission of important aspects and real difficulty drawing firm conclusions and cross study comparisons. A BO PROM encompassing non-dysplastic and dysplastic cohorts would solve these issues. A concise measure with a rapidly interpretable score could even be deployed in clinical practice to identify areas of focus for outpatient consultations.

The development of a new PROM requires a number of important stages (figure 6.1-1) (272). Prior to item generation and initial testing, a conceptual model should be formed. A conceptual model describes the elements of interest and how they may interact (273). This model is typically generated from a range of inputs. A literature review is required to gauge the depth in which the concept has already been studied including existing measures (274). Expert opinion can provide valuable insight into the key components' patients share, for example, the interview topic guide developed prior to the qualitative interviews. This is an important step to achieve content validity (275). Patient input is the final component of a robust conceptual model and often achieved via patient interviews or focus groups. This captures valuable in-depth data unmeasurable via quantitative methods and will give greater insight into the interactions between components. The literature review, qualitative (chapter 2) and quantitative (chapter 3) research presented in this thesis provides enough background data for the development of a BO PROM (276). Based on these findings a BO conceptual model should incorporate; gastroesophageal symptoms, worry of oesophageal cancer and burden of endoscopy. The interaction of disease specific knowledge with these factors should also be evaluated. A proposed conceptual model is depicted in figure 6.1-2

(272,277). Once finalised, items for a new PROM can be generated and initial validation testing can begin.

Figure 6.1-1 PROM Development

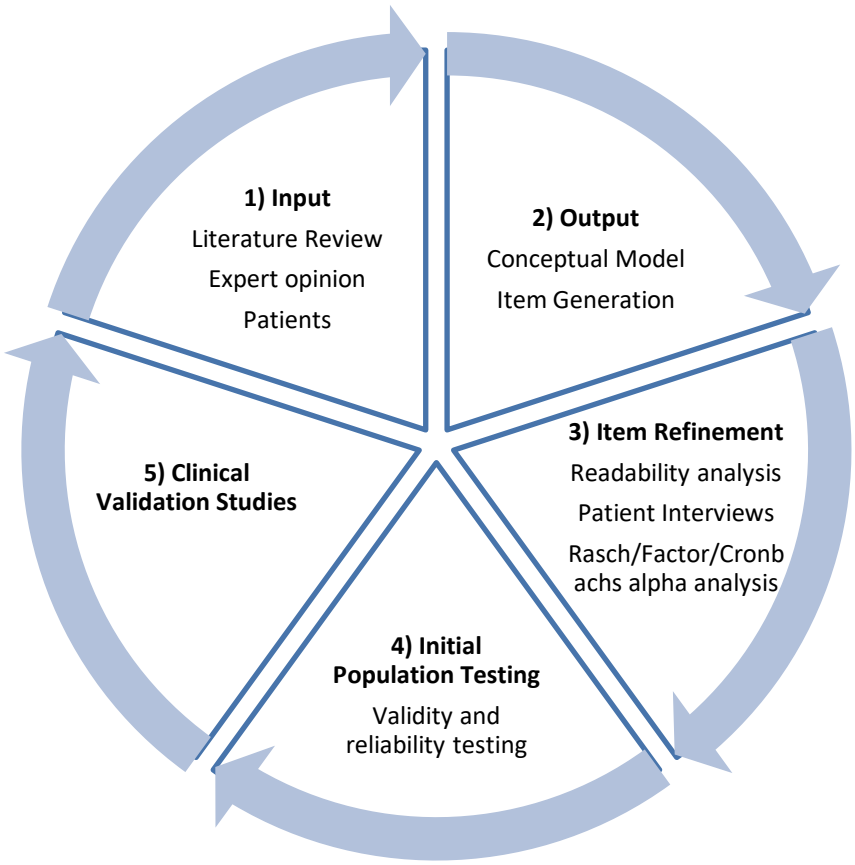
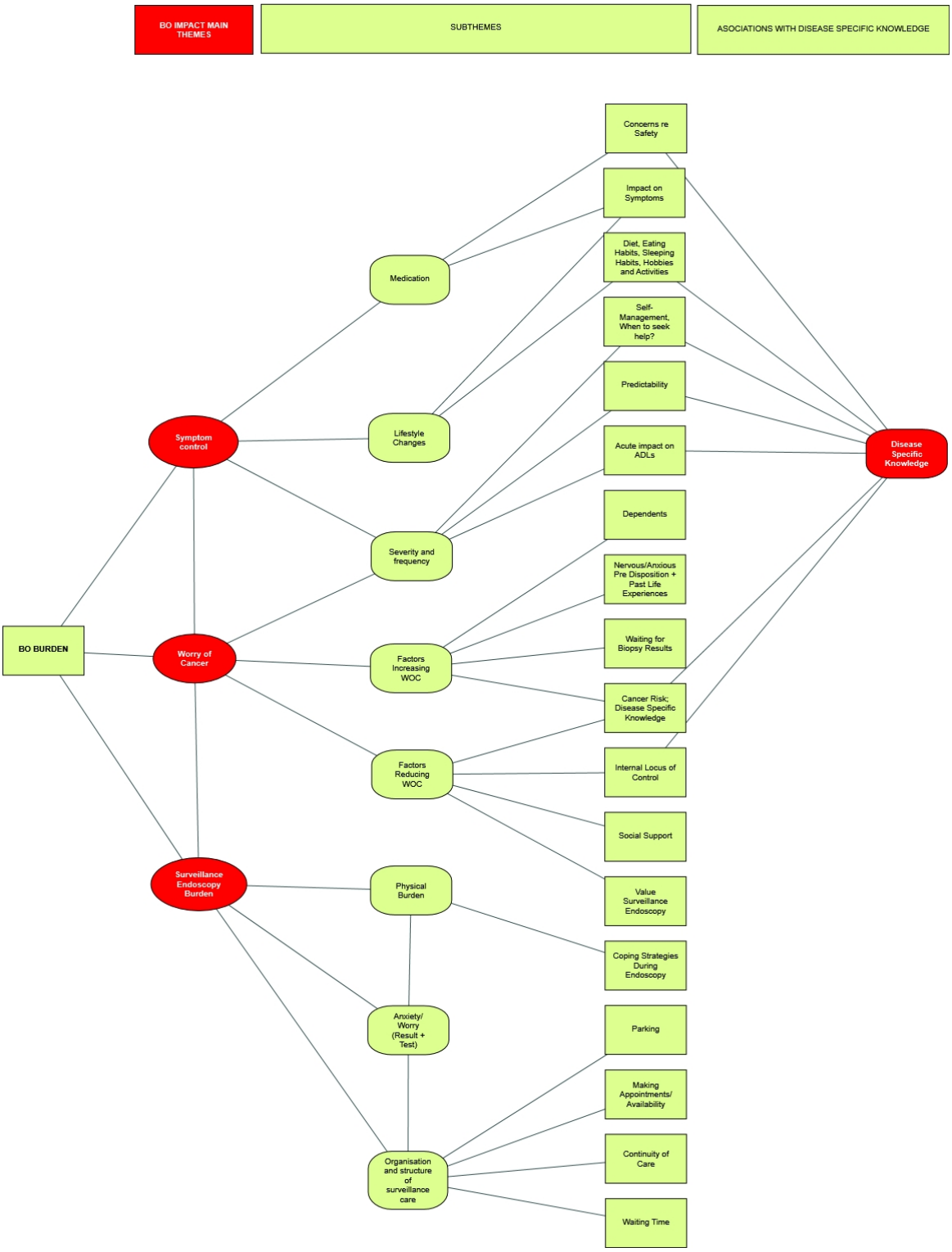


Figure 6.1-2 Barrett's oesophagus disease impact conceptual model



Undoubtedly patients with BO can carry a significant disease burden. This does not appear to be supported by standards of follow up care provision within the NHS. There is a clear appetite to develop care pathways with a stronger focus on dedicated services for BO patients. This was evident in both the qualitative research and broader research priority setting project (Chapter 4, priority number 4).

6.2. Barrett's oesophagus care pathways

Engagement of patients when setting research priorities is potentially a powerful medium to influence the direction of future research in their favour. Involvement of the research users at this primitive step is perhaps where their greatest influence can be realised. There are a number of key patient centric outcomes from this process that, if addressed, will reduce the burden of BO and GORD for patients in the future. Firstly, improved risk stratification for screening and surveillance purposes would reduce the need for invasive endoscopy for many patients. This is vitally important when one considers the acute psychological and physical implications of endoscopy reported in the in-depth interviews (chapter 2). The only caveat to this development is the reassuring aspect current BO patients experience from a negative endoscopy and the knowledge of "been kept an eye on". It is likely, in time, that patients will find newer methods of risk stratification equally reassuring when counselled appropriately. This process may be a key function of future dedicated BO clinics. Secondly, safe and effective long-term treatment of gastroesophageal reflux appears reflective of patients concerns over long term drug safety, a finding which was also prevalent in the patient interviews. This is also highly relevant to a significant minority of BO and GORD patients who respond poorly to PPI therapy and seek alternative long-term treatments. This is supported by the quantitative findings in chapter 3 which showed GORD patients are more likely to suffer worse symptom control than BO patients. The adjunct of effective alternative therapies and further research into PPI safety may decrease this burden for such patients. Finally, there is a clear need to assess and enhance current care provisions for BO patients by focusing them around a dedicated service. This was a key finding in both the qualitative interviews and the research priority setting exercise (priority number 4). In particular the qualitative research found follow up care was lacking in consistency, patient education, communication and organisation.

The final piece of research presented in this thesis is a proof of principal study designed to assess the potential benefits of a dedicated BO endoscopy service. This feasibility study focused on clinical outcome measures such as dysplasia detection and endoscopy quality rather than patient centred outcomes such as HRQOL and satisfaction. Although this study provides some insight into current care and potential benefits of dedicated endoscopy, in particular greater adherence to best practice guidelines, it is single centre in design and relatively small numbered to draw firm conclusions and generalisability. Further work is required to determine the true impact of a dedicated service on both clinical and patient centred outcomes. A service which encompasses direct secondary care access, surveillance endoscopy and clinic would be classified as a complex care intervention, "an intervention with several interacting components" (164). Much of the research presented in this thesis serves as preliminary and feasibility work necessary to develop such an intervention. The

multiple outcome measures, both clinical and patient centred, required to assess the overall efficacy of this intervention have also been identified.

6.3. Future research proposals in abstract format

6.3.1. Development and validation of a Barrett's oesophagus patient reported outcome measure.

Background. PROM's are an essential assessment of disease impact and efficacy of current and developing care pathways. BO has a number of potential disease specific impacts including GORD symptoms, worry of oesophageal cancer and burden of repeated endoscopies. There is no existing validated BO PROM therefore researchers currently rely upon multiple different generic instruments or instruments designed for other diseases such as GORD. This approach is cumbersome and makes cross study comparisons difficult. More concerningly it may lead to the inaccurate or under assessment of key HRQOL aspects pertinent to BO patients.

Aims. This study aims to develop and conduct the initial validity testing of a BO PROM. In particular;

- Conceptual model generation.
- Questionnaire item generation.
- Initial reliability and validity testing.

Methods. Input from prior literature review, expert opinion and in-depth patient interviews will be used to formulate a conceptual model. From this model an initial list of questionnaire items will be generated, each representing a single element. A recall period will be clearly defined and not too short to prevent capture of transient but significant impacts but not too long to prevent use in clinical trials. All items will be displayed in lay, easy to read English as a significant proportion of UK adults have insufficient literacy and numeracy to understand health related information (278). Readability will be formally assessed using validated tools such as the Flesch Reading Ease and Flesch-Kincaid Grade Level (279). Pre-testing will occur via a series of patient interviews which will facilitate item refinement by focusing on interpretation and appropriateness of each item. Reduction in item number will also be supported by factor analysis. The refined instrument will then undertake population testing using healthy, gastroesophageal reflux disease, non-dysplastic BO and dysplastic BO participants.

Results. The results from the population samples will allow further PROM refinement via psychometric testing. This will include validity (e.g. criterion and discriminative), reliability (e.g. test-retest, internal consistency) and responsiveness testing (272,277). Complete psychometric testing is likely to require multiple population samples and may ultimately be completed during use in clinical studies.

Conclusions. The successful development and validation of a BO PROM will allow for more simple, consistent and accurate assessments of patient centred outcomes.

6.3.2. Dedicated Endoscopy for Barrett's Oesophagus (DEBO study)

Background

The efficacy of endoscopic therapy for dysplasia and early OAC is now well established with increasingly durable long-term data (280). One major difficulty with BO is identifying those at risk of disease progression. Considering current research into individual risk stratification is likely to take years to reach routine clinical use surveillance endoscopy remains best practice for detecting change. A number of studies have focused their efforts on advanced endoscopic modalities to detect dysplasia more readily, with mixed results. One major issue with these techniques is the transferability out of tertiary centres and the additional training or equipment required (183).

Research, presented in this thesis, suggests the post-BSG guideline era of BO surveillance remains suboptimal in terms of patient needs and current best practice metrics. A dedicated service may improve the accuracy and consistency of surveillance care, although it remains unclear whether such a service can consistently improve clinical and patient centred outcomes. We propose a prospective, adequately powered, multicentre study to evaluate the role of a dedicated BO service which encompasses direct secondary care access and surveillance endoscopy.

Aims. This study aims to assess the efficacy of a dedicated BO surveillance service compared to current standards of practice. In particular;

- Adherence to best practice guidelines for Barrett's oesophagus surveillance and upper gastrointestinal endoscopy.
- Clinical outcome measures including; intestinal metaplasia, dysplasia and OAC diagnosis rates.
- Patient centred outcome measures, including satisfaction with services and health related quality of life.

Ethical Considerations and Consent. Ethical application ongoing.

Design and setting; A randomised prospective multicentre study is proposed. This study will be conducted solely within UK NHS hospitals and is designed to reflect and compare against real world practice.

Methods. Patients with BO will be recruited prior to their surveillance endoscopy and randomly routed to either a dedicated BO endoscopy list or normal service list. Dedicated lists will be conducted by a gastroenterologist or nurse endoscopist with a specialist interest in BO. The control group will be the normal service list which represents a real-world comparison and may be

undertaken by any JAG accredited endoscopist. Both study arms will be expected to use high definition white light endoscopy as outlined in the BSG guidelines. Use of further imaging modalities, such as narrow band imaging, will be at the discretion of the endoscopist on a case by case basis. After their endoscopy, participants in the dedicated arm will be provided with a direct access card. This "safety net" will allow participants to contact the dedicated BO service directly if they experience significant problems or concerns relating to their condition in between surveillance endoscopies. Considering the potential impact of this complex care intervention numerous outcome measures will be used and collected prospectively; 1) Key endoscopic performance indicators outlined in the BSG and AUGIS guidelines (1,269). 2) Clinical outcomes such as intestinal metaplasia, dysplasia and OAC detection rates. 3) Patient centred outcomes, including HRQOL measurement and patient satisfaction with services.

- Endoscopic performance data:
    - BSG endoscopic reporting dataset for BO surveillance
    - Hiatus hernia delineation (cm between diaphragmatic pinch and top of gastric folds)
    - Prague classification (CnMn)
    - Visible island description (size and distance from incisors)
    - Visible lesion description (Paris classification)
    - Seattle protocol biopsies (number and distance from incisors)
    - Oesophageal withdrawal time
    - Comfort scores
    - Sedation rates
    - Suspected endoscopic features of dysplasia and OAC e.g. Paris 2a/2c polyp
- Clinical Data:
    - Participant demographics including potential confounding factors such as co-morbidities, smoking status, BMI and family history of OAC.
    - Seattle protocol adherence (histology reported biopsy numbers)
    - Surveillance interval adherence
    - Histology results (intestinal metaplasia, dysplasia and OAC)
    - Discharges from surveillance (diagnosis ratification, preventing inappropriate surveillance)
- Health related quality of life data:

HRQOL measurement in this study will be undertaken using a newly developed BO specific PROM (development discussed above) and previously validated instruments. This will allow for reliability and validity testing of the new BO PROM. All participants will be asked to complete a

HRQOL questionnaire around the time of their surveillance test with a subset completing another in 3 months to assess consistency and durability of results. The usage of the direct access line will also be recorded prospectively (dedicated arm only).

Results and Analysis. We expect a dedicated service to hit key performance indicators and adhere to current best practice guidelines more readily and that this will translate into meaningful clinical and patient centred gains.

- Clinical outcome data and endoscopic performance metrics

Measured outcomes will be adherence to BSG guidelines for Barrett's surveillance as per the key endoscopic performance data listed above. We expect both study arms to be matched in terms of potential confounding factors such as age, sex, co-morbidities, Prague classification, smoking status and BMI. If the groups are not matched this may be accounted for within the analysis. Initial descriptive data will be expressed as means +/- standard deviations and percentiles. Comparison of the two-sample means will be determined by the closeness of the match and shapes of the distributions. A p value of <0.05 will be taken to show statistical significance.

- HRQOL data and PROM Validation

Descriptive statistics will be used to show the means, standard deviations and shapes of distributions for the variables of the instruments used. Initial analysis of subcategories will identify particular impacts, before comparing the two arms and assessing for relationships between variables. Propensity score matching will be used to control for confounding factors if the groups are not matched.

- Sample size

This complex care intervention requires numerous outcome measures which makes the required study sample size difficult to calculate exactly. However, we expect a medium to large number (500-800 in each group) to yield significant p values. For example, if we find the difference between the 2 groups dysplasia or OAC detection rate is 5% vs 2.5% the required sample to reach statistical significance is 711 (each group). This calculation in based on a 90% confidence interval (type 1 error) and power of 80% (type 2 error). In order to achieve these targets, we expect recruitment to take place from 3 sites across the north west with a view to opening 2 further sites from elsewhere in the UK via the clinical research network.

Conclusions. This research proposal will help decipher how best to deliver future BO surveillance care pathways whilst giving a more definitive insight into current, real-world, standards of practice.

6.3.3. The role of a dedicated Barrett's oesophagus clinic. A proof of principal randomised controlled trial

Introduction. The use of dedicated services to support patients with other chronic diseases is well established. Only recently has the BSG recommended all newly diagnosed BO patients are seen in a gastroenterology outpatient clinic (1). Historically a lack of evidence base surrounding surveillance has led to differing clinician views concerning BO which may have negatively impacted patient care (144). Research, presented in this thesis, suggests the post BSG guideline era of BO care remains poor. It is safe to assume the vast majority of BO patients undergoing surveillance have received very little professional interaction or disease specific information (145).

The BSG outlined a professional agenda for a BO new patient clinic, however this did not take into account patients' needs or expectations. The BSG admitted "further work is required to decipher how best to communicate this information to patients" (1). The qualitative research, in chapter 2, has delineated a more patient focused intervention in the form of a dedicated BO clinic which reflects patients' needs. A previous cohort study showed some clinical benefits of a dedicated BO clinic including changes to medication (17%) and cessation of surveillance (11%) (145). However, it remains unknown whether such a service can significantly improve patients' disease understanding, HRQOL and satisfaction with care provision.

Aims. To **a**ssess the effectiveness and practicality of a dedicated Barrett's oesophagus clinic.

Ethical Considerations and Consent. Prior ethical approval for this study was obtained from the Health Research Authority Yorkshire and Humber ethics committee (REC reference number 16/YH/0035). All participants will provide written consent.

Design and setting. A proof of principal randomised controlled trial is proposed. This study will be conducted solely within UK NHS hospitals.

Methods. All patients, able to give informed written consent, currently undergoing BO surveillance will be eligible to take part. New diagnoses will not be recruited for this study as ethically it would be inappropriate to randomise patients to solely endoscopic follow up without a clinic consultation. However, for reasons previously stated, the majority of patients have historically received little or no follow up care particularly those diagnosed before recent guideline publication (October 2013). Participants will be recruited at the time of their surveillance endoscopy and randomised to one of three groups;

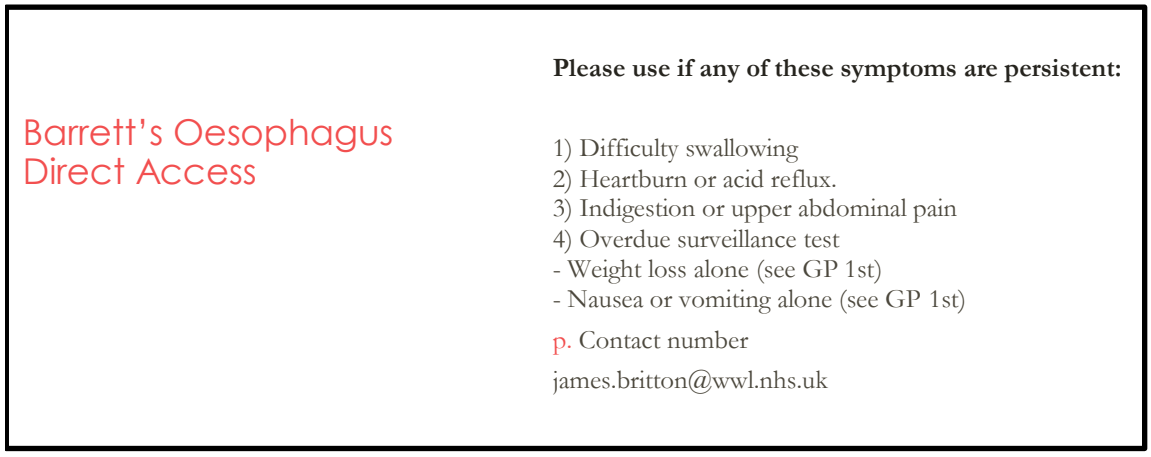
- Continued endoscopic surveillance plus a dedicated BO clinic consultation (intervention)
- Continued endoscopic surveillance only (control group 1)

- Continued endoscopic surveillance plus a general gastroenterology clinic follow up (control group 2)

Intervention; The Barrett's oesophagus clinic

- Organisation and structure:
    - Dedicated clinic delivered by a health care professional with a specialist interest in BO (clinical fellow, consultant gastroenterologist or nurse endoscopist).
    - 6-8 weeks after their endoscopy to allow time for histology reporting.
    - 20 minute "new patient" appointment time.
- The consultation
    - Two-way discussion with the aid of the patients own endoscopy pictures or drawings to enhance comprehension.
    - The consultation should cover both the professional agenda (outlined by the BSG) and patient agenda (outlined in chapter 2)
    - Patients should be offered additional material to take away. This may be in the form of an approved website (e.g. www.macmillan.org.uk/Cancerinformation/Cancertypes/Oesophagusgullet/Precancerousconditions/Barrettsoesophagus.aspx) or information leaflet (e.g. the BSG BO surveillance guideline appendix number 4). However, this information must not be a substitute for face to face discussion.
- Follow up and safety netting
    - Patients should be provided with a clear surveillance plan.
    - Patients should be provided with a direct access card and clear instructions of when to use it (figure 6.3.3-1).
    - This card has been created using the referral criteria defined by NICE for urgent and non-urgent suspected oesophageal cancer (281)

Figure 6.3.3-1 Barrett's Oesophagus Direct Access Card



Results and Analysis. The primary outcome measures will be participants satisfaction, HRQOL and disease specific knowledge. This will be measured with a questionnaire after clinic and again after 4 months. Other metrics such as changes to medication, preventing inappropriate surveillance may constitute secondary outcome measures. There is currently no comparative published studies or pilot studies assessing such an intervention. We predict a mid-size study of approximately 50-60 patients would be sufficient to identify a medium to large effect in scores and yield p values of <0.05.

Conclusion. We expect patients who attend the dedicated BO clinic to receive greater disease specific information for example, more counselling regarding cancer risk. This may in turn be associated with better HRQOL scores for example, reduced cancer specific worry. We also expect the dedicated BO clinic to adhere more closely to best practice guidelines when setting surveillance intervals and more proactive in discontinuing surveillance when clinically appropriate. A higher-powered multicentre follow on study may ultimately be needed to draw firmer more generalisable conclusions.

6.4. Conclusion

The carefully selected mixed methods research tools presented in this thesis has identified the key prevalent factors of BO disease burden. This work has also provided some insight into the interactions of these factors and efficacy of past and current care pathways. All the research papers in this thesis demonstrate there is a real need to enhance care pathways for BO patients. It appears that current care is lacking in meeting both patient needs and achieving best clinical practice metrics. Future developments must be more patient centric, structured, informative and consider the impact on HRQOL. Further work is needed to decipher whether improvements in care delivery, such as a dedicated BO service, can improve both key clinical outcomes and patient experiences.

In a broader sense, future research developments may significantly reduce the burden of this disease. Normally research direction is academically or industry driven, however, the patient and care provider engagement project presented in this thesis has given some power back to the research user. Hopefully, by setting their top research priorities this will influence funding and direction of research efforts in favour of patients.

7. References

1. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang J-Y, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2013 Oct 28;63(1):7–42.

2. Bennett C, Moayyedi P, Corley DA, DeCaestecker J, Falck-Ytter Y, Falk G, et al. BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia. The American Journal of Gastroenterology. 2015 Apr 14;110(5):662.

3. Eloubeidi MA, Mason AC, Desmond RA, El-Serag HB. Temporal trends (1973-1997) in survival of patients with esophageal adenocarcinoma in the United States: a glimmer of hope? The American Journal of Gastroenterology. 2003 Jul 23;98(7):1627–33.

4. Ronkainen J, Aro P, Storskrubb T, Johansson S-E, Lind T, Bolling-Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005 Dec 14;129(6):1825–31.

5. Zagari RM, Fuccio L, Wallander M-A, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut. 2008 Apr 18;57(10):1354–9.

6. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2011 Oct 13;61(7):970–6.

7. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011 Oct 15;365(15):1375–83.

8. Rebbeck TR, Domchek SM. Variation in breast cancer risk in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res. 2008 Jul 25;10(4):108.

9. Streitz JM, Andrews CW, Ellis FH. Endoscopic surveillance of Barrett's esophagus. Does it help? J Thorac Cardiovasc Surg. 1993 Mar 1;105(3).

10. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg. 1994 Nov 1;108(5).

11. van Sandick JW, van Lanschot JJ, Kuiken BW, Tytgat GN, Offerhaus GJ, Obertop H. Impact of endoscopic biopsy surveillance of Barrett‘s oesophagus on pathological stage and clinical outcome of Barrett’s carcinoma. Gut. 1999 Apr 6;43(2):216–22.

12. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. Gastroenterology. 2002 Mar 5;122(3):633–40.

13. Cooper GS, Yuan Z, Chak A, Rimm AA. Association of prediagnosis endoscopy with stage and survival in adenocarcinoma of the esophagus and gastric cardia. Cancer. 2002 Jul 13;95(1):32–8.

14. Fountoulakis A, Zafirellis KD, Dolan K, Dexter SPL, Martin IG, Sue-Ling HM. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg. 2004 Aug 3;91(8):997–1003.

15. Rubenstein JH, Sonnenberg A, Davis J, McMahon L, Inadomi JM. Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans. Gastrointest Endosc. 2008 Jun 11;68(5):849–55.

16. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. The American Journal of Gastroenterology. 2015 Nov 3;111(1):30–50.

17. Old O, Moayyedi P, Love S, Roberts C, Hapeshi J, Foy C et al. Barrett's Oesophagus Surveillance versus endoscopy at need Study (BOSS): protocol and analysis plan for a multicentre randomized controlled trial. Journal of Medical Screening. 2015;22(3):158.

18. Das A, Wells C, Kim HJ, Fleischer DE, Crowell MD, Sharma VK. An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. Endoscopy. 2009 May 5;41(5):400–8.

19. Somerville M, Garside R, Pitt M, Stein K. Surveillance of Barrett's oesophagus: is it worthwhile? Gastroenterology. 2008 Feb 12;44(4):588–99.

20. Sonnenberg A, Soni A, Sampliner RE. Medical decision analysis of endoscopic surveillance of Barrett's oesophagus to prevent oesophageal adenocarcinoma. Aliment Pharmacol Ther. 2002 Feb 22;16(1):41–50.

21. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. The American Journal of Gastroenterology. 1999 Aug 13;94(8):2043–53.

22. Pohl H, Sonnenberg A, Strobel S, Eckardt A, Rösch T. Endoscopic versus surgical therapy for early cancer in Barrett's esophagus: a decision analysis. Gastroenterology. 2009 Apr 25;70(4):623–31.

23. Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ. A cost-utility analysis of ablative therapy for Barrett's esophagus. Gastroenterology. 2009 Mar 6;136(7):062.

24. Hu Y, Puri V, Shami VM, Stukenborg GJ, Kozower BD. Comparative Effectiveness of Esophagectomy Versus Endoscopic Treatment for Esophageal High-grade Dysplasia. Ann Surg. 2015 Dec 18;263(4):719–26.

25. Hur C, Choi SE, Rubenstein JH, Kong CY, Nishioka NS, Provenzale DT, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. Gastroenterology. 2012 May 21;143(3):567–75.

26. Boger PC, Turner D, Roderick P, Patel P. A UK-based cost-utility analysis of radiofrequency ablation or oesophagectomy for the management of high-grade dysplasia in Barrett's oesophagus. Aliment Pharmacol Ther. 2010 Sep 13;32(11-12):1332–42.

27. Irvine EJ. Quality of life issues in patients with inflammatory bowel disease. The American Journal of Gastroenterology. 1997 Dec 12;92(12 Suppl):18S–24S.

28. Yacavone RF, Locke GR, Provenzale DT, Eisen GM. Quality of life measurement in gastroenterology: what is available? The American Journal of Gastroenterology. 2001 Mar 10;96(2):285–97.

29. Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut. 2000 Aug 15;47(3):444–54.

30. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993 Apr 15;118(8):622–9.

31. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994 Feb 1;106(2):287–96.

32. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care. 1981 Aug 1;19(8):787–805.

33. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E. The Nottingham Health Profile: subjective health status and medical consultations. Social science & medicine Part A, Medical sociology. 1981 May;15(3):221-229.

34. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Nov 5;16(3):199–208.

35. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun 11;30(6):473–83.

36. Grossi E, Groth N, Mosconi P, Cerutti R, Pace F, Compare A, et al. Development and validation of the short version of the Psychological General Well-Being Index (PGWB-S). Health Qual Life Outcomes. 2006 Nov 14;4:88.

37. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul 1;26(7):724–35.

38. Schmulson M, Lee OY, Chang L, Naliboff B, Mayer EA. Symptom differences in moderate to severe IBS patients based on predominant bowel habit. The American Journal of Gastroenterology. 1999 Oct 16;94(10):2929–35.

39. Eggleston A, Farup C, Meier R. The Domestic/International Gastroenterology Surveillance Study (DIGEST): design, subjects and methods. Scand J Gastroenterol Suppl. 1999 Nov 24;231:9–14.

40. Macran S, Wileman S, Barton G, Russell I. The development of a new measure of quality of life in the management of gastro-oesophageal reflux disease: the Reflux questionnaire. Qual Life Res. 2006 Oct 11;16(2):331–43.

41. Colwell HH, Mathias SD, Pasta DJ, Henning JM, Hunt RH. Development of a health-related quality-of-life questionnaire for individuals with gastroesophageal reflux disease: a validation study. Dig Dis Sci. 1999 Sep 18;44(7):1376–83.

42. Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988 Feb 1;33(2):129–34.

43. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmülling C, Neugebauer E, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg. 1995 Feb 1;82(2):216–22.

44. Raymond JM, Marquis P, Bechade D, Smith D, Fortunet HM, Poynard T, et al. [Assessment of quality of life of patients with gastroesophageal reflux. Elaboration and validation of a specific questionnaire]. Gastroenterol Clin Biol. 1999 Apr 29;23(1):32–9.

45. Velanovich V, Vallance SR, Gusz JR, Tapia FV, Harkabus MA. Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg. 1996 Sep 1;183(3):217–24.

46. Amouretti M, Nalet B, Robaszkiewicz M, Wainsten J-P, la Loge de C, Benmedjahed K, et al. Validation of the short-form REFLUX-QUAL (RQS), a gastro-esophageal reflux disease (GERD) specific quality of life questionnaire. Gastroenterol Clin Biol. 2005 Nov 19;29(8-9):793–801.

47. la Loge de C, Trudeau E, Marquis P, Kahrilas P, Stanghellini V, Talley NJ, et al. Cross-cultural development and validation of a patient self-administered questionnaire to assess quality of life in upper gastrointestinal disorders: the PAGI-QOL. Qual Life Res. 2005 Jan 18;13(10):1751–62.

48. Zéman Z, Rózsa S, Tihanyi T, Tarkó E. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). Surg Endosc. 2004 Dec 9;19(2):257–61.

49. Rush DR, Stelmach WJ, Young TL, Kirchdoerfer LJ, Scott-Lennox J, Holverson HE, et al. Clinical effectiveness and quality of life with ranitidine vs placebo in gastroesophageal reflux disease patients: a clinical experience network (CEN) study. J Fam Pract. 1995 Aug 1;41(2):126–36.

50. Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, van Zanten SV, et al. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). Eur J Surg Suppl. 1999 Feb 23;(583):41–9.

51. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009 May 29;360(22):2277–88.

52. Provenzale D. Health-related quality of life and severity of symptoms in patients with Barrett‘s esophagus and gastroesophageal reflux disease patients without Barrett’s esophagus. The American Journal of Gastroenterology. 2000;95(8):1881.

53. Lippmann QK, Crockett SD, Dellon ES, Shaheen NJ. Quality of life in GERD and Barrett's esophagus is related to gender and manifestation of disease. The American Journal of Gastroenterology. 2009 Sep 15;104(11):2695–703.

54. Madisch A, Miehlke S, Miehlke S, Sell S. Patients with Barrett's esophagus experience less reflux complaints. Gastroenterology. 2006;(130):A263–A263.

55. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 2003 Oct 11;18(8):767–76.

56. Willich SN, Müller-Nordhorn J, Kulig M, Binting S, Gohlke H, Hahmann H, et al. Cardiac risk factors, medication, and recurrent clinical events after acute coronary disease; a prospective cohort study. Eur Heart J. 2001 Feb 13;22(4):307–13.

57. Müller-Nordhorn J, Kulig M, Binting S, Völler H, Gohlke H, Linde K, et al. Change in quality of life in the year following cardiac rehabilitation. Qual Life Res. 2004 Apr 17;13(2):399–410.

58. Cooper SC, El-agib A, Dar S, Mohammed I, Nightingale P, Murray IA, et al. Endoscopic surveillance for Barrett‘s oesophagus: the patients’ perspective. Gut. 2009 Jul 15;21(8):850–4.

59. Crockett SD, Lipkus IM, Bright SD, Sampliner RE, Wang KK, Boolchand V, et al. Overutilization of endoscopic surveillance in nondysplastic Barrett's esophagus: a multicenter study. Gastrointest Endosc. 2011 Nov 17;75(1):23–31.e2.

60. Cullen J, Schwartz MD, Lawrence WF, Selby JV, Mandelblatt JS. Short-term impact of cancer prevention and screening activities on quality of life. J Clin Oncol. 2004 Mar 3;22(5):943–52.

61. Rosenberg RD, Yankaskas BC, Abraham LA, Sickles EA, Lehman CD, Geller BM, et al. Performance benchmarks for screening mammography. Radiology. 2006 Sep 23;241(1):55–66.

62. Curvers WL, Kate ten FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. The American Journal of Gastroenterology. 2010 May 11;105(7):1523–30.

63. Duits LC, Phoa KN, Curvers WL, Kate Ten FJW, Meijer GA, Seldenrijk CA, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2014 Jul 17;64(5):700–6.

64. Ganz RA, Allen JI, Leon S, Batts KP. Barrett‘s esophagus is frequently overdiagnosed in clinical practice: results of the Barrett’s Esophagus Endoscopic Revision (BEER) study. Gastrointest Endosc. 2013 Nov 18;79(4):565–73.

65. Levine DS, Blount PL, Rudolph RE, Reid BJ. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. The American Journal of Gastroenterology. 2000 May 16;95(5):1152–7.

66. Kruijshaar ME, Kerkhof M, Siersema PD, Steyerberg EW, Homs MYV, Essink-Bot M-L. The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus. Endoscopy. 2006 Oct 5;38(9):873–8.

67. Borkovec TD, Robinson E, Pruzinsky T, DePree JA. Preliminary exploration of worry: some characteristics and processes. Behav Res Ther. 1983 Jan 1;21(1):9–16.

68. Eysenck MW, Van Berkum J. Trait anxiety, defensiveness, and structure of worry. Personality

and Individual Differences. 1992 Jan 13(12):1285-1290.

69. Jensen JD, Bernat JK, Davis LA, Yale R. Dispositional cancer worry: convergent, divergent, and predictive validity of existing scales. J Psychosoc Oncol. 2010 Aug 24;28(5):470–89.

70. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979 May 1;41(3):209–18.

71. Gramling R, Anthony D, Frierson G, Bowen D. The cancer worry chart: a single-item screening measure of worry about developing breast cancer. Psychooncology. 2006 Nov 11;16(6):593–7.

72. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther. 1990 Jan 1;28(6):487–95.

73. Dijkstra A, Brosschot J. Worry about health in smoking behaviour change. Behav Res Ther. 2003 Aug 14;41(9):1081–92.

74. Gladstone GL, Parker GB, Mitchell PB, Malhi GS, Wilhelm KA, Austin M-P. A Brief Measure of Worry Severity (BMWS): personality and clinical correlates of severe worriers. J Anxiety Disord. 2004 Dec 29;19(8):877–92.

75. Tallis F, Davey GCL, Bond A. The Worry Domains Questionnaire. Worrying: Perspective on theory, assessment and treatment. New York: Wiley; 1994.

76. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. Health Psychol. 1991 Jan 1;10(4):259–67.

77. McCaul KD, Goetz PW. Worry. Health Behaviour Constructs: Theory, measurement and Research. http://cancercontrol.cancer.gov. (accessed April 2016).

78. Champion VL, Skinner CS, Menon U, Rawl S, Giesler RB, Monahan P, et al. A breast cancer fear scale: psychometric development. J Health Psychol. 2004 Sep 16;9(6):753–62.

79. Douma KFL, Aaronson NK, Vasen HFA, Gerritsma MA, Gundy CM, Janssen EPA, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psychooncology. 2009 Apr 22;19(3):289–98.

80. Pruzinsky T, Borkovec TD. Cognitive and personality characteristics of worriers. Behav Res Ther. 1990 Jan 1;28(6):507–12.

81. Stefanek M, Enger C, Benkendorf J, Honig SF, Lerman C. Bilateral prophylactic mastectomy decision making: A vignette study. Prev Med. 1999 Sep 10;29(3):216–21.

82. Katapodi MC, Lee KA, Facione NC, Dodd MJ. Predictors of perceived breast cancer risk and the relation between perceived risk and breast cancer screening: a meta-analytic review. Prev Med. 2004 Mar 17;38(4):388–402.

83. Hopwood P, Shenton A, Lalloo F, Evans DG, Howell A. Risk perception and cancer worry: an exploratory study of the impact of genetic risk counselling in women with a family history of breast cancer. J Med Genet. 2001 Apr 6;38(2):139.

84. Borgaonkar MR, Townson G, Donnelly M, Irvine EJ. Providing disease-related information worsens health-related quality of life in inflammatory bowel disease. Inflamm Bowel Dis. 2002 Jul 20;8(4):264–9.

85. Shaheen NJ, Peery AF, Hawes RH, Rothstein RI, Spechler SJ, Galanko JA, et al. Quality of life following radiofrequency ablation of dysplastic Barrett's esophagus. Endoscopy. 2010 Sep 30;42(10):790–9.

86. McCaul KD, Branstetter AD, Schroeder DM, Glasgow RE. What is the relationship between breast cancer risk and mammography screening? A meta-analytic review. Health Psychol. 1996 Nov 1;15(6):423–9.

87. Vernon SW. Risk perception and risk communication for cancer screening behaviors: a review. J Natl Cancer Inst Monographs. Oxford University Press; 2000 Jun 16;1999(25):101–19.

88. Shaheen NJ, Green B, Medapalli RK, Mitchell KL, Wei JT, Schmitz SM, et al. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology. 2005 Aug 9;129(2):429–36.

89. Kruijshaar ME, Siersema PD, Janssens ACJW, Kerkhof M, Steyerberg EW, Essink-Bot M-L. Patients with Barrett's esophagus perceive their risk of developing esophageal adenocarcinoma as low. Gastrointest Endosc. 2006 Dec 23;65(1):26–30.

90. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. Br J Psychiatry. 1976 Mar 1;128:280–9.

91. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed). 1986 Feb 1;292(6516):344.

92. Moorey S, Greer S, Watson M, Gorman C, Rowden L, Tunmore R, et al. The factor structure and factor stability of the hospital anxiety and depression scale in patients with cancer. Br J Psychiatry. 1991 Feb 1;158:255–9.

93. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997 Mar 1;27(2):363–70.

94. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-A review of validation data and clinical results. Journal of Psychosomatic Research. Jan 1997;42(1):17-41.

95. Essink-Bot M-L, Kruijshaar ME, Bac DJ, Wismans PJ, Borg ter F, Steyerberg EW, et al. Different perceptions of the burden of upper GI endoscopy: an empirical study in three patient groups. Qual Life Res. 2007 Jul 17;16(8):1309–18.

96. Moraca RJ, Low DE. Outcomes and health-related quality of life after esophagectomy for high-grade dysplasia and intramucosal cancer. Arch Surg. 2006 Jun 21;141(6):545.

97. Chang LC, Oelschlager BK, Quiroga E, Parra JD, Mulligan M, Wood DE, et al. Long-term outcome of esophagectomy for high-grade dysplasia or cancer found during surveillance for Barrett's esophagus. J Gastrointest Surg. 2006 Mar 1;10(3):341–6.

98. Headrick JR, Nichols FC, Miller DL, Allen MS, Trastek VF, Deschamps C, et al. High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy. Ann Thorac Surg. 2002 Jun 25;73(6).

99. Bennett C, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology. 2012 Apr 24;143(2):336–46.

100. Haidry RJ, Butt MA, Dunn JM, Gupta A, Lipman G, Smart HL, et al. Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut. 2014 Dec 24;64(8):1192–9.

101. Krishnamoorthi R, Singh S, Ragunathan K, Katzka DA, Wang KK, Iyer PG. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointest Endosc. 2016 Feb 20;83(6):1090–1106.e3.

102. Rosmolen WD, Boer KR, de Leeuw RJ, Gamel CJ, van Berge Henegouwen MI, Bergman JJ, et al. Quality of life and fear of cancer recurrence after endoscopic and surgical treatment for early neoplasia in Barrett's esophagus. Endoscopy. 2010 Jun 10;42(7):525–31.

103. Schembre D, Arai A, Levy S, Farrell-Ross M, Low D. Quality of life after esophagectomy and endoscopic therapy for Barrett's esophagus with dysplasia. Dis Esophagus. 2010;23(6):458.

104. National life tables, UK: 2013–2015. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015. (accessed Oct 2016).

105. Kemp K, Griffiths J, Campbell S, Lovell K. An exploration of the follow-up up needs of patients with inflammatory bowel disease. J Crohns Colitis. 2013 Mar 27;7(9):e386–95.

106. Jackson BD, Gray K, Knowles SR, De Cruz P. EHealth Technologies in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2016 Mar 1;10(9):1103–21.

107. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003 Feb 7;12(1):18–23.

108. Boivin A, Lehoux P, Lacombe R, Burgers J, Grol R. Involving patients in setting priorities for healthcare improvement: a cluster randomized trial. Implement Sci. 2014 Feb 20;9:24.

109. Elwyn G, Laitner S, Coulter A, Walker E, Watson P, Thomson R. Implementing shared decision making in the NHS. BMJ. 2010 Oct 14;341(oct14 2):c5146.

110. Davison BJ, Degner LF. Empowerment of men newly diagnosed with prostate cancer. Cancer Nurs. 1997 Jun 1;20(3):187–96.

111. Makarski J, Brouwers MC. The AGREE Enterprise: a decade of advancing clinical practice guidelines. Implement Sci. 2014 Aug 15;9:103.

112. Boivin A, Currie K, Fervers B, Gracia J, James M, Marshall C, et al. Patient and public involvement in clinical guidelines: international experiences and future perspectives. BMJ Qual Saf. 2010 Apr 27;19(5):e22.

113. Deyo RA, Cherkin DC, Weinstein J, Howe J, Ciol M, Mulley AG. Involving patients in clinical decisions: impact of an interactive video program on use of back surgery. Med Care. 2000 Sep 12;38(9):959–69.

114. Hunter J, Claridge A, James S, Chan D, Stacey B, Stroud M, et al. Improving outpatient services: the Southampton IBD virtual clinic. Frontline Gastroenterol. 2012 Mar 13;3(2):76–80.

115. Boivin A. The Guideline International Network Patient and Public Involvement Working Group. http://www.g-i-n.net/working-groups/gin-public/G-I-NPUBLIC. 2007.

116. Armstrong N, Herbert G, Aveling E-L, Dixon-Woods M, Martin G. Optimizing patient involvement in quality improvement. Health Expect. 2013 Feb 3;16(3):e36–47.

117. National Institute of Clinical Excellence. Patient and Public Involvement Policy.

https://www.nice.org.uk/media/default/About/NICE-Communities/Public-involvement/Patientand-

public-involvement-policy/Patient-and-public-involvement-policy-November-2013.pdf. 2013.

(accessed Nov 2016).

118. The James Lind Alliance. http://www.lindalliance.org. 2004. (accessed Nov 2016).

119. Mitton C, Smith N, Peacock S, Evoy B, Abelson J. Public participation in health care priority setting: A scoping review. Health Policy. 2009 Mar 3;91(3):219–28.

120. Stacey D, O'Connor AM, DeGrasse C, Verma S. Development and evaluation of a breast cancer prevention decision aid for higher-risk women. Health Expect. 2003 Feb 27;6(1):3–18.

121. Department of Health N. Health Equity and excellence: liberating the NHS.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213823/dh_11

7794.pdf. 2010. (accessed Nov 2016).

122. Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, et al. Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach. Health Technol Assess. 2004 Apr 15;8(15).

123. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. A systematic review of the impact of patient and public involvement on service users, researchers and communities. Patient. 2014 Jul 19;7(4):387–95.

124. Boivin A, Lehoux P, Burgers J, Grol R. What are the key ingredients for effective public involvement in health care improvement and policy decisions? A randomized trial process evaluation. Milbank Q. 2014 Jun 4;92(2):319–50.

125. Rowe G, Frewer LJ. A Typology of Public Engagement Mechanisms. Science, Technology and Human Values. 2005;30(2):251–90.

126. Fearon JD. Deliberation as discussion. Elster J, editor. Deliberative Democracy. Cambridge University Press; 1998;:44–68.

127. Abelson J, Forest P-G, Eyles J, Smith P, Martin E, Gauvin F-P. Deliberations about deliberative methods: issues in the design and evaluation of public participation processes. Soc Sci Med. 2003 May 27;57(2):239–51.

128. Dryzek JS. Legitimacy and Economy in Deliberative Democracy. Political Theory. 2001;29(5):651–69.

129. Gutmann A, Thompson D. Democracy and Disagreement. Cambridge: Harvard University Press; 1996. 1 p.

130. Ocloo J, Matthews R. From tokenism to empowerment: progressing patient and public involvement in healthcare improvement. BMJ Qual Saf. 2016 Mar 18;25(8):626–32.

131. Peat M, Entwistle V, Hall J, Birks Y, Golder S. Scoping review and approach to appraisal of interventions intended to involve patients in patient safety. J Health Serv Res Policy. 2010 Jan 28;15 Suppl 1(suppl 1):17–25.

132. Tritter JQ. Revolution or evolution: the challenges of conceptualizing patient and public involvement in a consumerist world. Health Expect. 2009 Sep 17;12(3):275–87.

133. Rutter D, Manley C, Weaver T, Crawford MJ, Fulop N. Patients or partners? Case studies of user involvement in the planning and delivery of adult mental health services in London. Soc Sci Med. 2004 Mar 17;58(10):1973–84.

134. Martin GP. Representativeness, legitimacy and power in public involvement in health-service management. Soc Sci Med. 2008 Oct 14;67(11):1757–65.

135. Collins HM, Evans R. The Third Wave of Science Studies: Studies of Expertise and Experience. Social Studies of Science. 2002 Apr;32(2):235–96.

136. Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. Lancet. 2000 Jul 8;355(9220):2037–40.

137. Cowan K, Oliver S. The James Lind Alliance guidebook. Oxford; 2016. 1 p.

138. National Institute for Health Research. National Institute for Health Research Relationship Statement (The James Lind Alliance). http://www.jla.nihr.ac.uk/about-the-james-lindalliance/using-the-jla-logo.htm. (accessed Nov 2016).

139. Buckley BS, Grant AM, Glazener CMA. Case study: a patient-clinician collaboration that identified and prioritized evidence gaps and stimulated research development. J Clin Epidemiol. 2011 Aug 4;66(5):483–9.

140. Elwyn G, Crowe S, Fenton M, Firkins L, Versnel J, Walker S, et al. Identifying and prioritizing uncertainties: patient and clinician engagement in the identification of research questions. J Eval Clin Pract. 2010 May 5;16(3):627–31.

141. Caygill CPJ, Royston C, Charlett A, Wall CM, Gatenby PAC, Ramus JR, et al. Mortality in Barrett's esophagus: three decades of experience at a single center. Endoscopy. 2012 Jul 2;44(10):892–8.

142. Solaymani-Dodaran M, Card TR, West J. Cause-specific mortality of people with Barrett's esophagus compared with the general population: a population-based cohort study. Gastroenterology. 2013 Apr 9;144(7):1375.

143. Sikkema M, de Jonge PJF, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009 Oct 20;8(3):235.

144. Mandal A, Playford RJ, Wicks AC. Current practice in surveillance strategy for patients with Barrett's oesophagus in the UK. Aliment Pharmacol Ther. 2003 May 21;17(10):1319–24.

145. Anagnostopoulos GK, Pick B, Cunliffe R, Fortun P, Kaye P, Ragunath K. Barrett's esophagus specialist clinic: what difference can it make? Dis Esophagus. 2006 Apr 29;19(2):84–7.

146. Redelmeier DA, Katz J, Kahneman D. Memories of colonoscopy: a randomized trial. Pain. 2003 Jul 12;104(1-2):187–94.

147. Arney J, Hinojosa-Lindsey M, Street RL, Hou J, El-Serag HB, Naik AD. Patient experiences with surveillance endoscopy: a qualitative study. Dig Dis Sci. 2014 Feb 6;59(7):1378–85.

148. Leach P, De Silva M, Mountifield R, Edwards S, Chitti L, Fraser RJL, et al. The effect of an inflammatory bowel disease nurse position on service delivery. J Crohns Colitis. 2013 Oct 22;8(5):370–4.

149. Bager P, Hentze R, Nairn C. Outpatients with inflammatory bowel disease (IBD) strongly prefer annual telephone calls from an IBD nurse instead of outpatient visits. Gastroenterol Nurs. 2013 Apr 4;36(2):92–6.

150. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin. 2012 Jan 4;62(2):118–28.

151. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. The American Journal of Gastroenterology. 2008 Oct 3;103(11):2694–9.

152. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010 May 25;19(6):1468–70.

153. Cancer Survival in England Adults diagnosed 2013-10-29.

https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddis

eases/bulletins/cancersurvivalinenglandadultsdiagnosed/2013-10-29. (accessed Jan 2018)

154. Be Clear on Cancer. www.nhs.uk/be-clear-on-cancer. (accessed Jan 2018).

155. Alexandropoulou K, van Vlymen J, Reid F, Poullis A, Kang J-Y. Temporal trends of Barrett's oesophagus and gastro-oesophageal reflux and related oesophageal cancer over a 10-year period in England and Wales and associated proton pump inhibitor and H2RA prescriptions: a GPRD study. Eur J Gastroenterol Hepatol. 2012 Oct 2;25(1):15–21.

156. Britton J, Keld R, Prasad N, Hamdy S, McLaughlin J, Ang Y. Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health-related quality of life. Lancet Gastroenterol Hepatol. 2017 Sep 29;.

157. Nemeth K, Shah V, Rasheed A. PTU-153 A Formal Surveillance Program with Dedicated Endoscopy Lists is Required to Improve Compliance with the British Society of Gastroenterology (BSG) Guidelines for Diagnosis and Management of Barrett'S Columnar-Lined Oesophagus. Gut. 2013 Jun;62(Suppl 1):A110–A111.

158. Hewlett S, de Wit M, Richards P, Quest E, Hughes R, Heiberg T, et al. Patients and professionals as research partners: challenges, practicalities, and benefits. Arthritis Rheum. 2006 Jul 29;55(4):676–80.

159. Mockford C, Staniszewska S, Griffiths F, Herron-Marx S. The impact of patient and public involvement on UK NHS health care: a systematic review. Int J Qual Health Care. 2011 Nov 22;24(1):28–38.

160. Experience-based design: from redesigning the system around the patient to co-designing services with the patient. 2006;15(5):307.

161. NHS Department of Health. Creating a Patient-led NHS.

http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consu

m_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4106507.pdf. 2005.

(accessed Jan 2018).

162. Probert CS, Mayberry JF. Inflammatory bowel disease: patients' expectations in the 1990s. J R Soc Med. 1991 Mar 1;84(3):131–2.

163. Ang Y. Quality of life measures in Barrett's Oesophagus care pathways. http://www.isrctn.com/ISRCTN76017289. 2017.

164. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 Sep 29;337:a1655.

165. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ. 1995 Jul 1;311(6996):42–5.

166. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007 Sep 14;19(6):349–57.

167. Patton M. Qualitative research & evaluation methods. 4th ed. California: Sage; 2015.

168. Bowling A. Research methods in Health. 2nd ed. Philadelphia: Open University Press, Maidenhead; 2002. 1 p.

169. Trotter RT. Qualitative research sample design and sample size: resolving and unresolved issues and inferential imperatives. Prev Med. 2012 Jul 16;55(5):398–400.

170. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2015 Nov 27;26(13):1753.

171. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Quality and Quantity. 2017 Sep;52(4):1893–907.

172. Ritchie J, Lewis J. Qualitative Research Practice: a guide for social science students and researchers. London: Sage; 2003. 1 p.

173. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013 Sep 18;13(1):117.

174. Bowling A. Research Methods in Health. 4th ed. New York, NY: Open University; 2014. 1 p.

175. Murphy SJ, Anderson LA, Johnston BT, Murray LJ. Patients with Barrett esophagus have poor understanding of the diagnosis and its implications. J Clin Gastroenterol. 2008 Feb 19;42(4):431–2.

176. Wardle RA, Mayberry JF. Patient knowledge in inflammatory bowel disease: the Crohn's and Colitis Knowledge Score. Eur J Gastroenterol Hepatol. 2013 Nov 13;26(1):1–5.

177. Selinger CP, Lal S, Eaden J, Jones DB, Katelaris P, Chapman G, et al. Better disease specific patient knowledge is associated with greater anxiety in inflammatory bowel disease. J Crohns Colitis. 2012 Oct 10;7(6):e214–8.

178. Eloubeidi MA, Provenzale D. Does this patient have Barrett‘s esophagus? The utility of predicting Barrett’s esophagus at the index endoscopy. The American Journal of Gastroenterology. 1999 Apr 14;94(4):937–43.

179. Selinger CP, Eaden J, Selby W, Jones DB, Katelaris P, Chapman G, et al. Patients' knowledge of pregnancy-related issues in inflammatory bowel disease and validation of a novel assessment tool (“CCPKnow”). Aliment Pharmacol Ther. 2012 May 9;36(1):57–63.

180. Eaden JA, Abrams K, Mayberry JF. The Crohn's and Colitis Knowledge Score: a test for measuring patient knowledge in inflammatory bowel disease. The American Journal of Gastroenterology. 1999 Dec 22;94(12):3560–6.

181. Sephton M, Kemp K, Ridgway V. An evaluation study of a pilot group education programme for inflammatory bowel disease. Frontline Gastroenterol. 2015 Oct 23;7(2):135–40.

182. Cuddy A. A systematic review of patient perspectives on surveillance after colorectal cancer treatment. J Cancer Surviv. 2017;11(5):542.

183. Naveed M, Dunbar KB. Endoscopic imaging of Barrett's esophagus. World J Gastrointest Endosc. 2016 Mar 17;8(5):259–66.

184. Jo Y, Park E, Ahn SB, Jo YK, Son B, Kim SH, et al. A Proton Pump Inhibitor's Effect on Bone Metabolism Mediated by Osteoclast Action in Old Age: A Prospective Randomized Study. Gut Liver. 2014 Dec 5;9(5):607–14.

185. Elkjaer M, Shuhaibar M, Burisch J, Bailey Y, Scherfig H, Laugesen B, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. Gut. 2010 Nov 13;59(12):1652–61.

186. Richards H, Emslie C. The 'doctor' or the 'girl from the University'? Considering the influence of professional roles on qualitative interviewing. Fam Pract. 2000 Feb 16;17(1):71–5.

187. A Systematic Review and Meta-Analysis of the Sex Ratio for Barrett's Esophagus, Erosive Reflux Disease, and Nonerosive Reflux Disease. 2005;162(11):1050.

188. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol. 2012 Jul 30;23(12):3155–62.

189. Britton J, Hamdy S, McLaughlin J, Horne M, Ang Y. Barrett's oesophagus: A qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect. 2018 Nov 14;.

190. Rosmolen WD, Nieuwkerk PT, Pouw RE, van Berge Henegouwen MI, Bergman JJGHM, Sprangers MAG. Quality of life and fear of cancer recurrence after endoscopic treatment for early Barrett's neoplasia: a prospective study. Dis Esophagus. 2016 Oct 21;.

191. Health Research Authority. http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf. 2017. (accessed Sept 2018).

192. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999 Mar 18;340(11):825–31.

193. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJW, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010 Apr 30;59(5):666–89.

194. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey manual and interpretation guide. Boston MA: The Health Institute; 1993. 1 p.

195. Maruish ME, editor. User's manual for the SF-36v2 Health Survey. Lincoln, RI; 2013.

196. Jenkinson C, Layte R, Lawrence K. Development and Testing of the Medical Outcomes Study 36-Item Short Form Health Survey Summary Scale Scores in the United Kingdom. Med Care. 1997;35(4):410.

197. Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. JSTOR. 1995;.

198. Jenkinson C. Comparison of UK and US methods for weighting and scoring the SF-36 summary measures. Journal of Public Health. 1999;21(4):372.

199. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ. 1993 May 29;306(6890):1437–40.

200. Bowling A, Bond M, Jenkinson C, Lamping DL. Short Form 36 (SF-36) Health Survey questionnaire: which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. J Public Health Med. 1999 Oct 21;21(3):255–70.

201. Prescott-Clarke P, Primatesta P, editors. Health survey for England. London; 1998.

202. Hobbs FDR, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK. Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. Eur Heart J. 2002 Nov 26;23(23):1867–76.

203. Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare. (accessed Sept 2018)

204. Burholt V, Nash P. Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. Journal of Public Health. 2011 Feb 9;33(4):587–603.

205. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pract. 1985 Apr 1;35(273):185–8.

206. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. Am J Public Health. 1979 Mar 1;69(3):238–45.

207. Locander W, Sudman S, Bradburn N. An Investigation of Interview Method, Threat and Response Distortion. Journal of the American Statistical Association. 1976 Jun;71(354):269–75.

208. Bowling A. Mode of questionnaire administration can have serious effects on data quality. Journal of Public Health. 2005 May 3;27(3):281–91.

209. Perkins JJ, Sanson-Fisher RW. An examination of self- and telephone-administered modes of administration for the Australian SF-36. J Clin Epidemiol. 1998 Nov 17;51(11):969–73.

210. Barry MJ, Walker-Corkery E, Chang Y, Tyll LT, Cherkin DC, Fowler FJ. Measurement of overall and disease-specific health status: does the order of questionnaires make a difference? J Health Serv Res Policy. 1995 Dec 9;1(1):20–7.

211. Lerman C, Daly M, Masny A, Balshem A. Attitudes about genetic testing for breast-ovarian cancer susceptibility. J Clin Oncol. 1994 Apr 1;12(4):843–50.

212. Custers JAE, van den Berg SW, van Laarhoven HWM, Bleiker EMA, Gielissen MFM, Prins JB. The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. Cancer Nurs. 2013 Mar 2;37(1):E44–50.

213. Custers JAE, Gielissen MFM, Janssen SHV, de Wilt JHW, Prins JB. Fear of cancer recurrence in colorectal cancer survivors. Support Care Cancer. 2015 Jun 25;24(2):555–62.

214. Lammens CRM, Bleiker EMA, Verhoef S, Hes FJ, Ausems MGEM, Majoor-Krakauer D, et al. Psychosocial impact of Von Hippel-Lindau disease: levels and sources of distress. Clin Genet. 2010 Feb 11;77(5):483–91.

215. Custers JAE, Kwakkenbos L, van de Wal M, Prins JB, Thewes B. Re-validation and screening capacity of the 6-item version of the Cancer Worry Scale. Psychooncology. 2018 May 29;.

216. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed). 1986 Feb 1;292(6516):344.

217. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. Journal of Psychosomatic Research. 2002 Feb 8;52(2):69–77.

218. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998 Mar 3;7(1):75–83.

219. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011 Jun 8;46(3):399–424.

220. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010 Sep 28;25(1):1–21.

221. Stata Statistical Software. 15th ed. StataCorp LLC.

222. Orman ES, Kim HP, Bulsiewicz WJ, Cotton CC, Dellon ES, Spacek MB, et al. Intestinal metaplasia recurs infrequently in patients successfully treated for Barrett's esophagus with radiofrequency ablation. The American Journal of Gastroenterology. 2012 Dec 18;108(2).

223. Shaheen NJ, Overholt BF, Sampliner RE, Wolfsen HC, Wang KK, Fleischer DE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011 May 6;141(2):460–8.

224. Rubenstein JH, Scheiman JM, Sadeghi S, Whiteman D, Inadomi JM. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: synthesis and estimates from population studies. The American Journal of Gastroenterology. 2010 Dec 7;106(2):254–60.

225. Atkin W, Wooldrage K, Brenner A, Martin J, Shah U, Perera S, et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. Lancet Oncol. 2017 Apr 28;18(6):823–34.

226. Delaney B. Is society losing control of the medical research agenda? BMJ. 2006 Mar 17;332(7549):1063–4.

227. Jun M, Manns B, Laupacis A, Manns L, Rehal B, Crowe S, et al. Assessing the extent to which current clinical research is consistent with patient priorities: a scoping review using a case study in patients on or nearing dialysis. Can J Kidney Health Dis. 2015 Oct 1;2:35.

228. Crowe S, Fenton M, Hall M, Cowan K, Chalmers I. Patients', clinicians“ and the research communities” priorities for treatment research: there is an important mismatch. Research Involvement and Engagement. 2015 Jun;.

229. Chalmers I, Rounding C, Lock K. Descriptive survey of non-commercial randomised controlled trials in the United Kingdom, 1980-2002. BMJ. 2003 Nov 1;327(7422):1017.

230. Coleman HG, Bhat S, Murray LJ, McManus D, Gavin AT, Johnston BT. Increasing incidence of Barrett's oesophagus: a population-based study. Eur J Epidemiol. 2011 Jun 14;26(9):739–45.

231. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995 Aug 5;311(7001):376–80.

232. Wiseman EF, Ang YS. Risk factors for neoplastic progression in Barrett's esophagus. World J Gastroenterol. 2011 Oct 13;17(32):3672–83.

233. Anderson LA, Murray LJ, Murphy SJ, Fitzpatrick DA, Johnston BT, Watson RGP, et al. Mortality in Barrett's oesophagus: results from a population based study. Gut. 2003 Jul 17;52(8):1081–4.

234. Gordon LG, Mayne GC, Hirst NG, Bright T, Whiteman DC, Watson DI. Cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's esophagus. Gastrointest Endosc. 2013 Sep 27;79(2):242–56.e6.

235. Findlay JM, Middleton MR, Tomlinson I. Genetic Biomarkers of Barrett's Esophagus Susceptibility and Progression to Dysplasia and Cancer: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2015 Oct 7;61(1):25–38.

236. Gregson EM, Bornschein J, Fitzgerald RC. Genetic progression of Barrett's oesophagus to oesophageal adenocarcinoma. Br J Cancer. 2016 Jul 21;115(4):403–10.

237. Parasa S, Vennalaganti S, Gaddam S, Vennalaganti P, Young P, Gupta N, et al. Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia. Gastroenterology. 2017 Dec 19;154(5):1282–1289.e2.

238. Kunzmann AT, Thrift AP, Johnston BT, McManus DT, Gavin AT, Turkington RC, et al. External validation of a model to determine risk of progression of Barrett's oesophagus to neoplasia. Aliment Pharmacol Ther. 2019 Apr 4;49(10):1274–81.

239. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol. 2013 Sep 4;27(3):443–54.

240. Heidelbaugh JJ, Metz DC, Yang Y-X. Proton pump inhibitors: are they overutilised in clinical practice and do they pose significant risk? Int J Clin Pract. 2012 May 23;66(6):582–91.

241. Hopkins J, Switzer NJ, Karmali S. Update on novel endoscopic therapies to treat gastroesophageal reflux disease: A review. World J Gastrointest Endosc. 2015 Sep 1;7(11):1039–44.

242. Das B, Reddy M, Khan OA. Is the Stretta procedure as effective as the best medical and surgical treatments for gastro-oesophageal reflux disease? A best evidence topic. Int J Surg. 2016 Apr 5;30:19–24.

243. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014 Oct 18;13(6):1058–67.e1.

244. Liang W-T, Wang Z-G, Wang F, Yang Y, Hu Z-W, Liu J-J, et al. Long-term outcomes of patients with refractory gastroesophageal reflux disease following a minimally invasive endoscopic procedure: a prospective observational study. BMC Gastroenterol. 2014 Oct 10;14(1):178.

245. Saino G, Bonavina L, Lipham JC, Dunn D, Ganz RA. Magnetic Sphincter Augmentation for Gastroesophageal Reflux at 5 Years: Final Results of a Pilot Study Show Long-Term Acid Reduction and Symptom Improvement. J Laparoendosc Adv Surg Tech A. 2015 Oct 5;25(10):787–92.

246. Soffer E, Rodríguez L, Rodriguez P, Gómez B, Neto MG, Crowell MD. Effect of electrical stimulation of the lower esophageal sphincter in gastroesophageal reflux disease patients refractory to proton pump inhibitors. World J Gastrointest Pharmacol Ther. 2016 Feb 9;7(1):145–55.

247. Rodríguez L, Rodriguez P, Gómez B, Ayala JC, Oxenberg D, Perez-Castilla A, et al. Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease. Surgery. 2014 Nov 6;157(3):556–67.

248. Kappelle WFW, Bredenoord AJ, Conchillo JM, Ruurda JP, Bouvy ND, van Berge Henegouwen MI, et al. Electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-

oesophageal reflux disease - interim results of an international multicentre trial. Aliment Pharmacol Ther. 2015 Jul 8;42(5):614–25.

249. Håkansson B, Montgomery M, Cadiere GB, Rajan A, Varannes des SB, Lerhun M, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther. 2015 Oct 13;42(11-12):1261–70.

250. Testoni PA, Mazzoleni G, Testoni SGG. Transoral incisionless fundoplication for gastro-esophageal reflux disease: Techniques and outcomes. World J Gastrointest Pharmacol Ther. 2016 May 10;7(2):179–89.

251. Haidry RJ, Lipman G, Banks MR, Butt MA, Sehgal V, Graham D, et al. Comparing outcome of radiofrequency ablation in Barrett's with high grade dysplasia and intramucosal carcinoma: a prospective multicenter UK registry. Endoscopy. 2015 Jun 30;47(11):980–7.

252. Belghazi K, Cipollone I, Bergman JJGHM, Pouw RE. Current Controversies in Radiofrequency Ablation Therapy for Barrett's Esophagus. Curr Treat Options Gastroenterol. 2016 Feb 20;14(1):1–18.

253. Shaheen NJ, Greenwald BD, Peery AF, Dumot JA, Nishioka NS, Wolfsen HC, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc. 2010 Apr 7;71(4):680–5.

254. Peerally MF, Barr H, Lovat L, Bhandari P, Ragunath K, Smart HL, et al. BRIDE (Barrett‘s Randomised Intervention for Dysplasia by Endoscopy) -Results of a Feasibility Study Comparing Argon Plasma Coagulation (APC) With Radiofrequency Ablation (RFA) After Endoscopic Resection of Patients With High Grade Dysplasia or T1 Adenocarcinoma in Barrett’s Esophagus. Gastrointest Endosc. 2016 May;83(5):AB151.

255. Pasricha S, Bulsiewicz WJ, Hathorn KE, Komanduri S, Muthusamy VR, Rothstein RI, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol. 2014 May 9;12(11):1840–7.e1.

256. Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AspECT and BOSS trials provide an evidence base. BMJ. 2006 Jun 24;332(7556):1512.

257. Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. Recent Results Cancer Res. 2009 Feb 14;181:161–9.

258. Deane KHO, Flaherty H, Daley DJ, Pascoe R, Penhale B, Clarke CE, et al. Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease. BMJ Open. 2014 Dec 14;4(12):e006434.

259. Hart AL, Lomer M, Verjee A, Kemp K, Faiz O, Daly A, et al. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. J Crohns Colitis. 2016 Aug 9;11(2):204–11.

260. Adler RH. The lower esophagus lined by columnar epithelium. Its association with hiatal hernia, ulcer, stricture, and tumor. J Thorac Cardiovasc Surg. 1963 Jan 1;45:13–34.

261. Hawe A, Payne WS, Weiland LH, Fontana RS. Adenocarcinima in the columnar epithelial lined lower (Barret) oesophagus. Thorax. 1973 Jul 1;28(4):511–4.

262. Haggitt RC, Tryzelaar J, Ellis FH, Colcher H. Adenocarcinoma complicating columnar epithelium-lined (Barrett's) esophagus. Am J Clin Pathol. 1978 Jul 1;70(1):1–5.

263. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau J-M, Esteban J-M, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017 Jan 25;49(2):191–8.

264. Britton J, Gadeke L, Lovat L, Hamdy S, Hawkey C, McLaughlin J, et al. Research priority setting in Barrett's oesophagus and gastro-oesophageal reflux disease. Lancet Gastroenterol Hepatol. 2017 Sep 1;2(11):824–31.

265. Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus--the need for standardization of the definition and of endoscopic criteria. The American Journal of Gastroenterology. 1998 Jul 22;93(7):1033–6.

266. Ooi J, Wilson P, Walker G, Blaker P, DeMartino S, O'Donohue J, et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy. 2017 Apr 11;49(6):524–8.

267. Valori R. How many 'points' should there be on an endoscopy list? www.thejag.org.uk. 2012.

268. Gupta N, Gaddam S, Wani SB, Bansal A, Rastogi A, Sharma P. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. Gastrointest Endosc. 2012 Jun 23;76(3):531–8.

269. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Pritchard DM, et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). Gut. 2017 Aug 18;66(11):1886–99.

270. Abrams JA, Kapel RC, Lindberg GM, Saboorian MH, Genta RM, Neugut AI, et al. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. Clin Gastroenterol Hepatol. 2009 Jan 13;7(7):736.

271. Harrison R, Perry I, Haddadin W, McDonald S, Bryan R, Abrams K, et al. Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. The American Journal of Gastroenterology. 2007 Apr 13;102(6):1154–61.

272. Rothrock NE, Kaiser KA, Cella D. Developing a valid patient-reported outcome measure. Clin Pharmacol Ther. 2011 Oct 5;90(5):737–42.

273. Earp JA, Ennett ST. Conceptual models for health education research and practice. Health Educ Res. 1991 May 9;6(2):163–71.

274. Klem M, Saghafi E, Abromitis R, Stover A, Dew MA, Pilkonis P. Building PROMIS item banks: librarians as co-investigators. Qual Life Res. 2009 Jun 23;18(7):881–8.

275. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: developing best practices based on science and experience. Qual Life Res. 2009 Sep 27;18(9):1263–78.

276. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009 Mar 5;25(4):929–42.

277. Pesudovs K, Burr JM, Harley C, Elliott DB. The development, assessment, and selection of questionnaires. Optom Vis Sci. 2007 Aug 19;84(8):663–74.

278. Rowlands G, Protheroe J, Winkley J, Richardson M, Seed PT, Rudd R. A mismatch between population health literacy and the complexity of health information: an observational study. Br J Gen Pract. 2015 May 27;65(635):e379–86.

279. Kincaid JP, Fishburne RP, Rogers RL, Chissom BS. Derivation of New Readability Formulas (Automated Readability Index, Fog Count and Flesch Reading Ease Formula) for Navy Enlisted Personnel: Chief of Naval Technical training. Memphis Naval Air Station; 1975.

280. Haidry R, Lovat L. Long-term durability of radiofrequency ablation for Barrett's-related neoplasia. Curr Opin Gastroenterol. 2015 Jun 4;31(4):316–20.

281. National Institute of Clinical Excellence guidelines. nice.org.uk/pathways/suspected-cancer-recognition-and-referral. https://pathways.nice.org.uk/pathways/suspected-cancer-recognition-and-referral. 2018. (accessed Nov 2018).

8. Supplementary appendix

8.1. Chapter 2

8.1.1. Consolidated Criteria for Reporting Qualitative studies (COREQ) 32-item checklist.

Table 8.1.1-1: Consolidated Criteria for Reporting Qualitative studies (COREQ) 32-item checklist (domain 1: research team and reflexivity)

No. Item	Description	Reported in section
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Interviews were conducted by JB	2.2.3
2. Credentials	JB; Post graduate (MBChB) PhD student. SH; Professor of Neurogastroenterology (non-Barrett's specialist) and honorary consultant Gastroenterologist. JM; Professor of Gastroenterology and Nutrition (non-Barrett's specialist) and honorary consultant Gastroenterologist. MH; Associate professor. Main research expertise in qualitative and mixed methods research. Clinical background in primary care, community and public health nursing. YA; Professor in Gastroenterology (oesophageal diseases) and Consultant Gastroenterologist and Honorary reader with specialist interest in Barrett's oesophagus.	NA
3. Occupation	As listed above	NA
4. Gender	JB; Male SH; Male JM; Male MH; Female YA; Male	NA
5. Experience and training	JB Training in Qualitative Research includes: - Manchester University Tutorials - SRA Qualitative data analysis - Guidance from academic supervisors/senior authors	NA
Relationship with participants		
6. Relationship established	Prior to recruitment participants and researcher had not met.	2.2.2
7. Participant knowledge of the interviewer	Participants were made aware that JB was a doctor doing post graduate research.	2.2.3 and 2.4.1
8. Interviewer characteristics	Participants were made aware of the interviewer's characteristics (doctor and researcher). The potential impact of this on the data collected has been reflected upon. All authors backgrounds have been included in this checklist and the manuscript includes a COI statement.	2.4.1

Table 8.1.1-2: Consolidated Criteria for Reporting Qualitative studies (COREQ) 32-item checklist (domain 2: study design)

Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	Framework analysis approach	2.2
Participant selection	Patients undergoing BO surveillance were recruited to achieve maximum variation in terms of age, gender, sex and disease duration	Table 2.3-1
10. Sampling	Purposive sampling	2.2.2
11. Method of approach	Face-to-face, telephone or mail.	2.2.2
12. Sample size	20	2.3
13. Non-participation	20 Participants 45 Declined to participate (reasons not explored) 0 Dropped out	NA
Setting		
14. Setting of data collection	At the workplace in a private seminar room	2.2.3
15. Presence of non-participants	None	NA
16. Description of sample	Participant demographics and characteristics reported include; Age, gender, disease duration, Prague classification and co-morbidities.	Table 2.3-1
Data collection		
17. Interview guide	The topic guide was devised from prior literature review and expert opinion.	2.2.3 and appendix 7.1.2
18. Repeat interviews	None	NA
19. Audio/visual recording	All interviews were audio recorded and transcribed verbatim.	2.2.3
20. Field notes	Field notes were made during the interview.	2.2.3
21. Interview duration	Average= 40 mins Range= 21-76 mins	2.2.3
22. Data saturation	Data saturation occurred at 20 interviews	2.3
23. Transcripts returned	Transcripts were not returned to participants for comment/correction	NA

Table 8.1.1-3: Consolidated Criteria for Reporting Qualitative studies (COREQ) 32-item checklist (domain 3: analysis and findings)

Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	2 authors (JB and MH)	2.2.5
25. Description of the coding tree	Table 1 outlines the conceptual framework (main themes and initial categories) with the number of contributing participants and verbatim quotes linked to each item.	Table 2.2.4-1
26. Derivation of themes	The initial themes, which formulated the conceptual framework, were derived from the first 4 interviews and topic guide.	2.2.4
27. Software	NVivo Pro 11	2.2.4
28. Participant checking	No participant feedback on the findings	NA
Reporting		
29. Quotations presented	Participant quotations are embedded in the results section. Each quotation is linked to a unique participant ID	2.3
30. Data and findings consistent	There was consistency between the data presented and the findings.	2.3
31. Clarity of major themes	Major themes are clearly presented	2.3 and 2.5
32. Clarity of minor themes	Diverse findings/cases are included in throughout the results section	2.3

8.1.2. Topic Guide

Introduction

- Explain no wright/wrong answers and the need to record the discussion
- Discuss confidentiality
- Explain this research forms part of a larger study exploring the impact Barrett's Oesophagus and its care pathways on patients.

Objectives

- Develop a greater understanding of the patient's viewpoint in relation to their diagnosis and care.
- Explore what factors related to Barrett's Oesophagus affect patients Quality of life.
- Identify any particular problems patients with Barrett's Oesophagus may experience.
- Identify any particular problems patients experience with their follow up care
- Help us explore ways of improving their follow up care.
- Identify what is important to them in their follow up and how they would change their care.

Background Information

- Participant introduces themselves (sound check)
- Include age, gender, co-morbidities and disease duration.

Exploring the Patient Burden of Barrett's Oesophagus

Summary of Topics/Discussion prompts.

- **Impact on General Health.** Explore any negative or positive issues raised. Probe into why they have these beliefs or feelings. How have these experiences affected them? How have they coped with any negative experiences?

    a. How do you consider your current general health? What concerns, if any, do you have?
    b. How has your health changed since you have been diagnosed with Barrett's Oesophagus?

- **The impact of Physical Symptoms.** Explore any impact on activities of daily living including work, leisure, sleep, relationships etc.). Probe into how these symptoms may have affected them and how have they coped with any negative experiences?

    a. How do you control your symptoms related to Barrett's Oesophagus (i.e. GORD)?
    b. In what ways have you had to change your lifestyle? (eating habits, smoking, alcohol)
    c. Do you ever have any problems or concerns regarding the medication you take for Barrett's Oesophagus?
    d. What typically happens when you experience breakthrough/uncontrolled symptoms?
    e. How important is adequate symptom control to you? (may need to ask patients to think back to pre-diagnosis/pre-medication)

- **The Psychological Burden.** Explore any impact on activities of daily living including work, leisure, sleep, relationships etc.). Probe into why they have these beliefs or feelings and how these experiences may have affected them. How have they coped with any negative experiences?

    a. What concerns or worries do you have relating to Barrett's Oesophagus?
    b. How do you perceive the risk of developing Oesophageal cancer in people with Barrett's Oesophagus?
    c. How do you perceive your own risk of developing Oesophageal cancer?
    d. How else has a diagnosis of Barrett's Oesophagus affected your mental health?

- **The Burden of Endoscopic Surveillance?** Explore any positive and negative issues raised. Probe into why they have these beliefs or feeling and how these experiences may have affected them. How have they coped with any negative experiences?

    a. What concerns, if any, do you have regarding the need for repeated endoscopies?
    b. What aspect/s do you find the most burdensome? (Explore before, during and after the test)
    c. How important are surveillance endoscopies to you?

d. If your next surveillance endoscopy was missed or late how would this affect you?
e. How would you feel if someone said you no longer required endoscopy check-ups?

Exploring the follow up needs of patients with Barrett's Oesophagus

Summary of Topics/Discussion Prompts

- **Experience of follow up care at diagnosis**. Explore positive and negative issues and how these experiences have impacted them. Probe into why they have these beliefs or feelings. How have they coped with any negative experiences raised?

    a. What occurred at the time of initial diagnosis? Probe: What concerns, if any, did you have and explain further…
    b. How were you followed up?
    c. What did you want or need at this time?
    d. How did you receive information about your diagnosis and future surveillance? (at endoscopy, clinic, leaflet, self-educated)
    e. Did they engage with their GP for support or advice? Explore any barriers.
    f. Probe: Who provided this information? Did you feel the information provided was adequate? If not, why not? Explain further?
    g. Overall was this follow up adequate enough? Were you provided/equipped with everything you needed regarding Barrett' Oesophagus? (such as knowledge, medication, lifestyle advice, symptom control etc).

- **Experience of follow up care now**. Explore positive and negative issues and how these experiences impacted them. Probe into why they have these beliefs or feelings. How have they coped with any negative experiences raised?

    a. Typically, what happens with your current follow up?
    b. How important is follow up care to you now?
    c. How have your needs changed from diagnosis to now?
    d. How important is the "doctor-patient" face to face relationship? Explore both primary/secondary care.
    e. How satisfied are you with your current follow up arrangement?

- **Changes to current follow up care**. Explore any knowledge of alternative methods. (If no knowledge then describe alternatives to generate discussion e.g. direct access line, virtual clinics, open access patient initiated appointments etc.)

    a) If you developed breakthrough symptoms or concerns regarding your Barrett's Oesophagus how would you manage this?
    b) At what point would you ask for help and who would you contact?
    c) Have you considered any other means of follow up?
    d) What do you think about a specialist Barrett's Oesophagus service? (clinic and endoscopy)
    e) What do you think about patient-initiated appointments?
    f) What do you think about telephone consultations or online remote "virtual" clinics?
    g) What would you change about the current follow up system? (Explore where, how, by whom and why)

Summary Question: Are we missing anything. Is there anything else that I have failed to ask you in this interview which you feel is important for me to know?

8.1.3. Conceptual framework codebook with descriptions

Table 8.1.3-1 Codebook 1-2

Name of Nodes	Description	Sources	References
1) Controlling Symptoms			
Impact of Medication on symptoms	This theme highlights the impact of medication on participants reflux related symptoms. It includes participants recollection of their symptoms prior to diagnosis and treatment.	18	40
Changes to Lifestyle	This theme explores the participants changes to their lifestyle since diagnosis. This includes dietary measures, eating habits and sleeping arrangements for example.	20	68
Managing symptom flare ups	Although patients by and large report reasonable/good symptom control their symptoms do seem to "flare up" occasionally. This theme explores what happened during these episodes and how participants deal with them.	19	40
Concerns regarding medication	Patients with Barrett's oesophagus face lifelong PPI therapy. This theme explores any concerns or adverse effects participants may have experienced.	19	31
2) Disease Impact			
Physical symptom impact	This theme evaluates the prevalence and impact of participants physical symptoms on their day to day life for example; their hobbies, work, relationships, social occasions and sleep.	18	59
Psychological impact	This theme evaluates the prevalence and potential impact of psychosocial symptoms related to Barrett's oesophagus, particularly relating to the risk of cancer. This theme explores if any worries or concerns regarding cancer have caused significant anxiety/depression or effected day to day life e.g. Hobbies, work, relationships, social occasions or sleep.	20	106
Surveillance endoscopy impact	This theme addresses the acute impact of a surveillance endoscopy. This encompasses both the physical burden of the test and also any worries/anxieties leading up to the test.	19	65

Table 8.1.3-2: Codebook 3-4

Name of Nodes	Description	Sources	References
3) Disease Specific Knowledge			
Disease specific knowledge and health beliefs	Historically patients with Barrett's oesophagus have received little or no disease specific information. This theme explores their knowledge relating to Barrett's and perhaps how this may influence their health behaviour.	20	96
Knowledge gaps	Historical follow up care has perhaps left patients with limited disease specific knowledge, this theme draws attention to the gaps in participants knowledge and what their needs are in terms of further information.	16	68
Information sources	This theme highlights the various sources of information participants have received and which sources are more desirable and why.	19	78
4) Follow up Experiences			
Experiences with secondary care at time of diagnosis.	This theme identifies participants experiences of secondary care at the time of their diagnosis paying particular attention to how, where, and when they were told about Barrett's oesophagus.	20	71
Experiences of surveillance endoscopy	This theme highlights participants experiences of their surveillance endoscopies. This encompasses their experiences and expectations of what occurs before, during and after the test.	19	81
Experiences with primary care (GP)	This theme explores participants experiences with primary care relating to their Barrett's oesophagus. This theme pays particular attention to the role of primary care in managing symptoms/"flare ups" and providing adequate disease specific information.	19	50
Value of surveillance endoscopy to them	Considering the lack of an RCT demonstrating the efficacy of surveillance do patients over value its worth. What would be their response to a missed test or advice to stop surveillance altogether.	19	62

Table 8.1.3-3 Codebook 5-6

Name of Nodes	Description	Sources	References
5) Follow up Needs			
Unmet needs	Historical follow up care has been unstructured and perhaps conducted by poorly informed or disengaged physicians due to a lack of evidence base. Has this left patients with significant unmet needs follow up needs that? These nodes explore those needs.	18	62
Value of seeing an expert	This theme explores how much participants value an expert opinion from their past experiences or expectations from their follow up care.	12	31
Other ideas offered	This theme highlights other follow up changes/suggestions from the participants.	14	37
6) Attitudes to new models of follow up care. (This theme explores the participants views on suggested changes to follow up care aimed to address their unmet needs)			
Dedicated Barrett's oesophagus service	This change to follow up care encompasses a dedicated Barrett's surveillance endoscopy list and Barrett's outpatient clinic. We expect such a service could improve continuity of care, quality and consistency of endoscopy, patient disease specific knowledge and satisfaction.	20	77
Patient initiated telephone consultation	This suggested change to follow up care offers a safety net for patients between their surveillance endoscopies. Some participants experience significant and worrying symptoms within this timeframe (2-5yrs). This direct access line offers support, advice and quicker access to hospital appointments or tests if required.	20	78
Patient initiated online consultation	This suggested change to follow up care offers a safety net for patients between their surveillance endoscopies. Some participants experience significant and worrying symptoms within this timeframe (2-5yrs). This online "virtual clinic" offers support, advice and quicker access to hospital appointments or tests if required.	18	39

8.1.4. Thematic chart

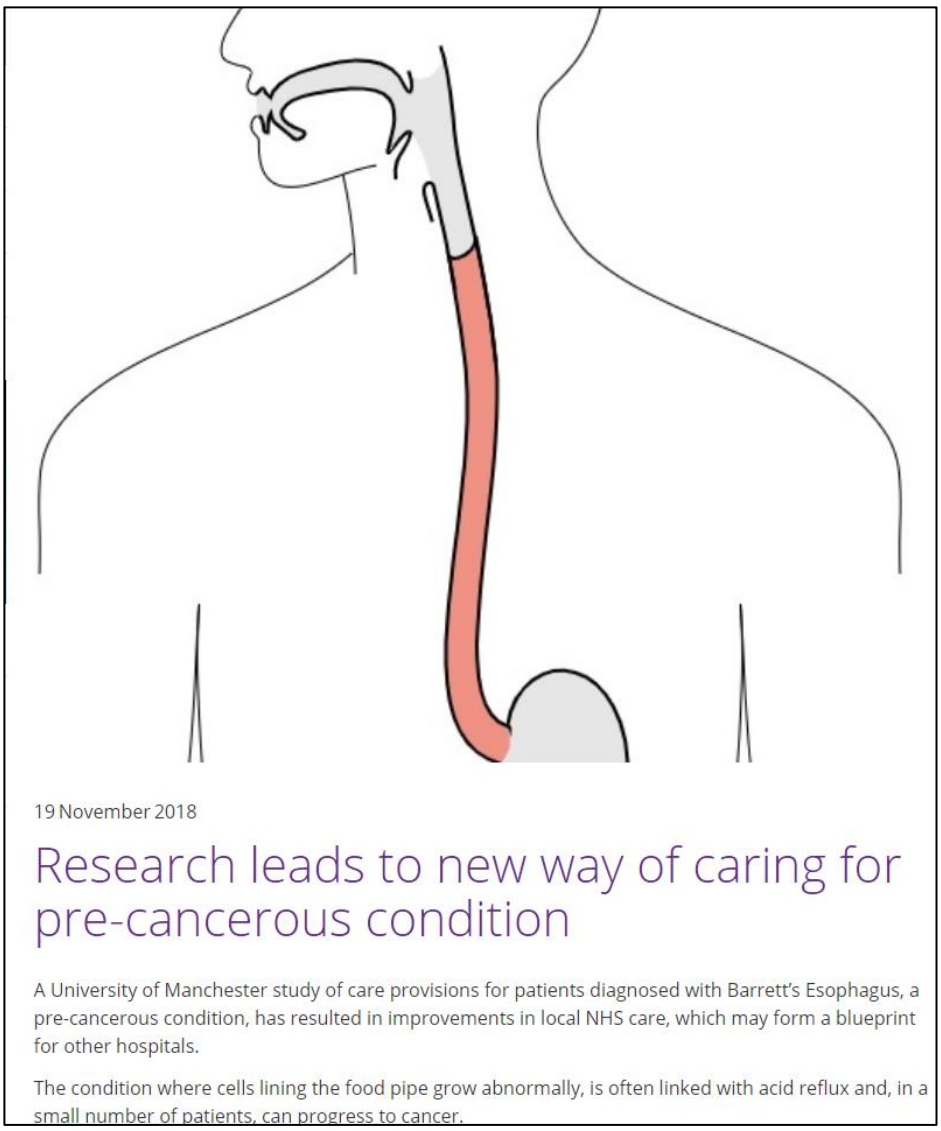
Table 8.1.4-1 Example of a thematic chart (disease impact)

	Sub-Themes		
Responder	**2.1 Physical symptom impact**	**2.2 Associated worries or anxieties**	**2.3 Surveillance endoscopy impact**
A	"I thought I'm not putting up with it because…..I sing in a choir and I felt it was affecting me"		
B		"I don't worry about it. What will be, will be. And if it's not that bad I'm not going to worry about it"	
C			"once or twice when the camera twists it makes you gurgle, it's like you're choking"
D	"I struggle when say you're going out with friends and it comes on, it's hard to explain, you can't go around and tell them, you just need to go home and you just feel like you want to be sick."		

For an example of a fully indexed thematic chart please see the supplementary USB material

8.1.5. Dissemination of results; University of Manchester Press Release

Figure 8.1.5-1 University of Manchester Press Release



19 November 2018

Research leads to new way of caring for pre-cancerous condition

A University of Manchester study of care provisions for patients diagnosed with Barrett's Esophagus, a pre-cancerous condition, has resulted in improvements in local NHS care, which may form a blueprint for other hospitals.

The condition where cells lining the food pipe grow abnormally, is often linked with acid reflux and, in a small number of patients, can progress to cancer.

https://www.manchester.ac.uk/discover/news/research-leads-to-new-way-of-caring-for-pre-cancerous-condition/

Research leads to new way of caring for pre-cancerous condition

A University of Manchester study of care provisions for patients diagnosed with Barrett's Oesophagus, a pre-cancerous condition, has resulted in improvements in local NHS care, which may form a blueprint for other hospitals.

The condition where cells lining the food pipe grow abnormally, is often linked with acid reflux and, in a small number of patients, can progress to cancer.

Barrett's is the only known precursor to a type of cancer called oesophageal adenocarcinoma which, unlike most other cancers, is currently increasing in the number of people affected every year.

Patients diagnosed with Barrett's have been identified as a key at-risk group for monitoring to improve early diagnosis rates for oesophageal cancer.

The study, led by Dr James Britton, found that provisions and support for patients diagnosed with this condition were inadequate.

Due to insufficient and inconsistent care, many patients felt poorly informed with some lacking confidence in their ability to self-manage their condition.

The study was supported by Covidien and led by researchers based at Wrightington, Wigan and Leigh NHS Foundation Trust and The University of Manchester.

Patients spoke to researchers about their condition and treatment experiences in semi-structured and in-depth one-to-one interviews.

He said "Listening to patients' experiences and concerns has contributed towards significant changes in care provisions for Barrett's patients at this NHS trust, with a dedicated service now in place."

If caught early, oesophageal adenocarcinomas are treatable via minimally invasive endoscopic techniques. This treatment is very effective and durable with only 1-2% of patients subsequently developing invasive cancer.

However, prognosis is very poor if the condition is not caught early.

Long-term monitoring means that these patients need to undergo regular invasive endoscopic procedures, which can have a significant impact on their quality of life.

"These patients carry a heavy burden of regular invasive procedures, symptom flare-ups, and worry of disease progression to cancer" Says Dr Britton.

"Despite this burden, they remain a forgotten patient group. Many don't receive adequate information about their condition and their care is often inconsistent with no central lynchpin.

This current standard of practice for Barrett's patients is likely to be endemic across NHS hospitals"

The minority of patients in this study who self-reported as having adequate knowledge of their condition and its implications, showed a lower tendency towards cancer-related worries.

This suggests that well informed patients are less likely to experience reduced quality of life due to chronic and unnecessary cancer related worry.

"This should be the norm" states Dr Britton

Patient-centred care and tailoring services around patient's needs has already led to improved care for patients living with other chronic conditions, for example Inflammatory Bowel Disease.

These improvements have been shown to enhance patient self-management of disease flares, reduce hospital admissions, GP appointments and hospital appointments leading to large cost savings.

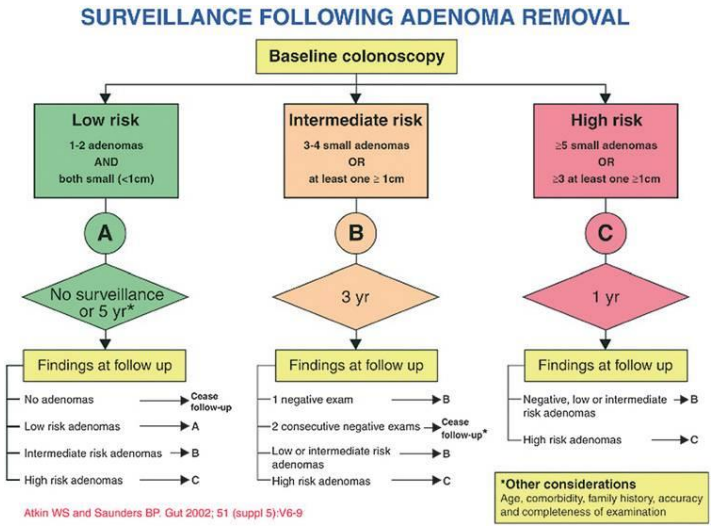
Dr Britton added "We found a clear appetite for a Barrett's focused services which could bridge the gap between GP and hospital care; providing information and dedicated patient support between surveillance tests"

"We now want to take our findings to other hospitals. We hope that a large multi-centre study will enable us to influence clinical guidelines and provisions for Barrett's care across the UK, and improve more patients' experiences with this condition."

8.2. Chapter 3

8.2.1. Supplementary figures

Figure 8.2.1-1 BSG Colonic Adenoma Risk Stratification and Surveillance Guidelines



8.2.2. Supplementary tables

Table 8.2.2-1 SF 36 quantitative data quality indicators. Missing Data and Data quality

	Completeness of items. (Target ≥90%) N=687	**Consistency of responses** (response consistency index) (Target ≥90% with an RCI score of 0)	**Percentage of estimable scale scores** (Target 90%) (10 estimable scale scores per respondent)	**Scale Reliability** (Target 100% of scales with a Cronbach's alpha ≥0.7)
SF-36 Total **PF (10 items)** **RP (4 items)** **BP (2 items)** **GH (5 items)** **VT (4 items)** **SF (2 items)** **RE (3 items)** **MH (5 items)** **(8 domains, 2 summary scores)**	97.8%	88.5%	98.1%	100% 0.94 0.97 0.90 0.85 0.87 0.89 0.96 0.86
GSRS Total **(15 items)**	95.4%	Na	Na	0.85
HADS Total **(14 items, 2 domains)**	96.2%	Na	Na	0.92
CWS **(6 items)**	97.0%	Na	Na	0.93

Table 8.2.2-2 Barrett's oesophagus responder and non-responder demographics

	Non-dysplastic Barrett's oesophagus Responder N= 306	**Non-dysplastic Barrett's oesophagus Non-Responder N= 460**	**p Value**
Age	64.6	63.6	P=0.222
Sex (%Male)	64.7%	74.8%	P=0.003*
Co-morbidities			
None	29.4%	57.0%	
1-2 Co-morbidities	54.2%	38.1%	
3-4 Co-morbidities	16.0%	4.9%	
5 or more Co-morbidities	0.3%	0.0%	
Prague Classification (M)	3.6	3.3	P=0.100

P values derived from independent t test

Table 8.2.2-3 Co-morbidity subcategories

	Non-dysplastic Barrett's oesophagus. N= 306	Dysplastic Barrett's oesophagus (post-ET). N= 49	Gastroesophageal reflux disease. N= 132	Colonic Adenoma. N= 152	Non-dysplastic BO (Non-responders) N= 460
Cardiovascular Disease	13.7%	20.4%	13.6%	17.8%	11.4%
Cerebrovascular Disease	5.2%	12.2%	0.8%	5.3%	1.1%
Peripheral Vascular Disease	1.6%	0.0%	0.0%	0.7%	1.3%
Diabetes	11.1%	34.7%	14.4%	21.1%	8.3%
Chronic Kidney Disease	1.0%	0.0%	0.0%	1.3%	0.9%
Chronic Lung Disease	20.9%	18.4%	15.2%	23.7%	16.1%
Musculoskeletal Disease	36.9%	55.1%	35.6%	44.1%	7.2%
Mental Health Disorder	18.0%	16.3%	33.3%	18.4%	7.8%
Neurological Disease	1.3%	4.1%	1.5%	1.3%	2.5%
Gastrointestinal Disease	11.4%	18.4%	25.8%	15.1%	2.9%
Cancer (prior/inactive)	7.5%	8.2%	9.8%	10.5%	3.1%

Cohort diagnoses included in each co-morbidity category. Cardiovascular disease; angina, ischaemic heart disease, coronary artery bypass graft, myocardial infarction. Cerebrovascular disease; transient ischaemic attack, stroke. Peripheral vascular disease; peripheral vascular disease, abdominal aortic aneurysm. Diabetes; type 1 and 2 diabetes. Chronic kidney disease; chronic kidney disease, nephrotic syndrome. Chronic lung disease; Chronic obstructive pulmonary disease, asthma, bronchiectasis, obstructive sleep apnoea. Musculoskeletal disease; osteoarthritis, rheumatoid arthritis, gout, chronic joint or back pain, fibromyalgia, chronic fatigue syndrome, ankylosing spondylitis, acromegaly, connective tissue disease, amyloidosis. Mental health disorder; anxiety, depression, post traumatic distress disorder, schizophrenia. Neurological disease; multiple sclerosis, Parkinson's disease, epilepsy, chronic subdural haematoma, spina bifida, myasthenia gravis. Gastrointestinal disease; irritable bowel syndrome, inflammatory bowel disease, diverticular disease, coeliac disease, intestinal failure, previous gastrointestinal surgery, primary biliary cirrhosis, non-alcoholic fatty liver disease. Cancer (prior or inactive); breast, colorectal, bladder, lymphoma, skin (squamous cell carcinoma, melanoma), stomach, oesophageal, prostate, uterine, leukaemia, ovarian, thyroid, lung. Reported co-morbidities excluded; Prior pulmonary embolism, permanent pacemaker, basil cell carcinoma, renal stone disease, hypertension, hyperlipidaemia, atrial fibrillation, hypothyroidism, migraine.

Table 8.2.2-4 Gastrointestinal symptom rating scale item responses (items 1-10)

		Non-dysplastic Barrett's oesophagus.	Dysplastic Barrett's oesophagus (post-ET).	Gastroesophageal reflux disease/dyspepsia.	Colonic Adenoma.
1) Abdominal pains	None	63.9% (189)	72.7% (32)	56.1% (69)	69.6% (96)
	Mild	23.0% (68)	18.2% (8)	24.4% (30)	20.3% (28)
	Moderate	11.8% (35)	9.1% (4)	17.1% (21)	8.0% (11)
	Severe	1.4% (4)	0.0% (0)	2.4% (3)	2.2% (3)
2) Heartburn	None	62.9% (185)	71.1% (32)	39.1% (50)	78.2% (111)
	Mild	25.9% (76)	26.7% (12)	29.7% (38)	15.5% (22)
	Moderate	7.8% (23)	0.0% (0)	21.1% (27)	3.5% (5)
	Severe	3.4% (10)	2.2% (1)	10.2% (13)	2.8% (4)
3) Acid Regurgitation	None	63.3% (190)	71.7% (33)	50.4% (64)	81.6% (115)
	Mild	26.7% (80)	23.9% (11)	24.4% (31)	15.6% (22)
	Moderate	6.0% (18)	4.3% (2)	16.5% (21)	2.1% (3)
	Severe	4.0% (12)	0.0% (0)	8.7% (11)	0.7% (1)
4) Hunger Pains	None	74.2% (219)	84.4% (38)	66.7% (84)	85.9% (122)
	Mild	16.3% (48)	8.9% (4)	18.3% (23)	11.3% (16)
	Moderate	7.5% (22)	4.4% (2)	12.7% (16)	2.1% (3)
	Severe	2.0% (6)	2.2% (1)	2.4% (3)	0.7% (1)
5) Nausea	None	83.6% (249)	93.3% (42)	65.4% (83)	90.8% (128)
	Mild	12.8% (38)	4.4% (2)	27.6% (35)	9.2% (13)
	Moderate	2.0% (6)	2.2% (1)	5.5% (7)	0.0% (0)
	Severe	1.7% (5)	0.0% (0)	1.6% (2)	0.0% (0)
6) Rumbling	None	60.1% (179)	69.8% (30)	48.4% (62)	69.4% (100)
	Mild	29.5% (88)	25.6% (11)	39.8% (51)	22.2% (32)
	Moderate	9.1% (27)	2.3% (1)	9.4% (12)	7.6% (11)
	Severe	1.3% (4)	2.3% (1)	2.3% (3)	0.7% (1)
7) Abdominal Bloating	None	57.1% (169)	75.6% (34)	50.0% (64)	67.6% (98)
	Mild	26.4% (78)	17.8% (8)	32.0% (41)	23.4% (34)
	Moderate	12.5% (37)	4.4% (2)	11.7% (15)	6.9% (10)
	Severe	4.1% (12)	2.2% (1)	6.3% (8)	2.1% (3)
8) Belching	None	55.4% (165)	56.5% (26)	37.2% (48)	73.1% (106)
	Mild	33.6% (100)	37.0% (17)	37.2% (48)	24.8% (36)
	Moderate	10.1% (30)	4.3% (2)	18.6% (24)	1.4% (2)
	Severe	1.0% (3)	2.2% (1)	7.0% (9)	0.7% (1)
9) Increased Flatus	None	48.8% (146)	43.5% (20)	35.1% (46)	53.4% (78)
	Mild	37.1% (111)	41.3% (19)	37.4% (49)	37.7% (55)
	Moderate	10.4% (31)	10.9% (5)	20.6% (27)	7.5% (11)
	Severe	3.7% (11)	4.3% (2)	6.9% (9)	1.4% (2)
10) Decreased Stools	None	61.2% (175)	61.7% (29)	46.5% (59)	63.3% (88)
	Mild	13.3% (38)	19.1% (9)	22.0% (28)	15.1% (21)
	Moderate	4.2% (12)	2.1% (1)	3.1% (4)	2.2% (3)
	Severe	21.3% (61)	17.0% (8)	28.3% (36)	19.4% (27)

Table 8.2.2-4 Gastrointestinal symptom rating scale item responses (items 11-15)

		Non-dysplastic Barrett's oesophagus.	Dysplastic Barrett's oesophagus (post-ET).	Gastroesophageal reflux disease/dyspepsia.	Colonic Adenoma.
11) Increased Stools	None	87.8% (252)	91.5% (43)	84.3% (107)	89.9% (125)
	Mild	6.3% (18)	0.0% (0)	10.2% (13)	5.8% (8)
	Moderate	4.5% (13)	2.1% (1)	3.1% (4)	2.2% (3)
	Severe	1.4% (4)	6.4% (3)	2.4% (3)	2.2% (3)
12) Loose Stools	None	69.5% (205)	62.2% (28)	56.9% (70)	76.2% (109)
	Mild	23.7% (70)	33.3% (15)	33.3% (41)	17.5% (25)
	Moderate	4.4% (13)	4.4% (2)	6.5% (8)	4.2% (6)
	Severe	2.4% (7)	0.0% (0)	3.3% (4)	2.1% (3)
13) Hard Stools	None	74.2% (219)	73.3% (33)	57.7% (71)	77.6% (111)
	Mild	16.3% (48)	17.8% (8)	25.2% (31)	13.3% (19)
	Moderate	5.8% (17)	4.4% (2)	7.3% (9)	6.3% (9)
	Severe	3.7% (11)	4.4% (2)	9.8% (12)	2.8% (4)
14) Urgency	None	65.2% (191)	57.8% (26)	56.1% (69)	63.4% (90)
	Mild	26.3% (77)	31.1% (14)	35.0% (43)	29.6% (42)
	Moderate	7.5% (22)	11.1% (5)	7.3% (9)	6.3% (9)
	Severe	1.0% (3)	0.0% (0)	1.6% (2)	0.7% (1)
15) Incomplete Evacuation	None	54.4% (160)	46.7% (21)	41.5% (51)	59.2% (84)
	Mild	34.7% (102)	48.9% (22)	42.3% (52)	33.1% (47)
	Moderate	8.5% (25)	2.2% (1)	8.9% (11)	4.9% (7)
	Severe	2.4% (7)	2.2% (1)	7.3% (9)	2.8% (4)

Table 8.2.2-5 Cancer worry scale.

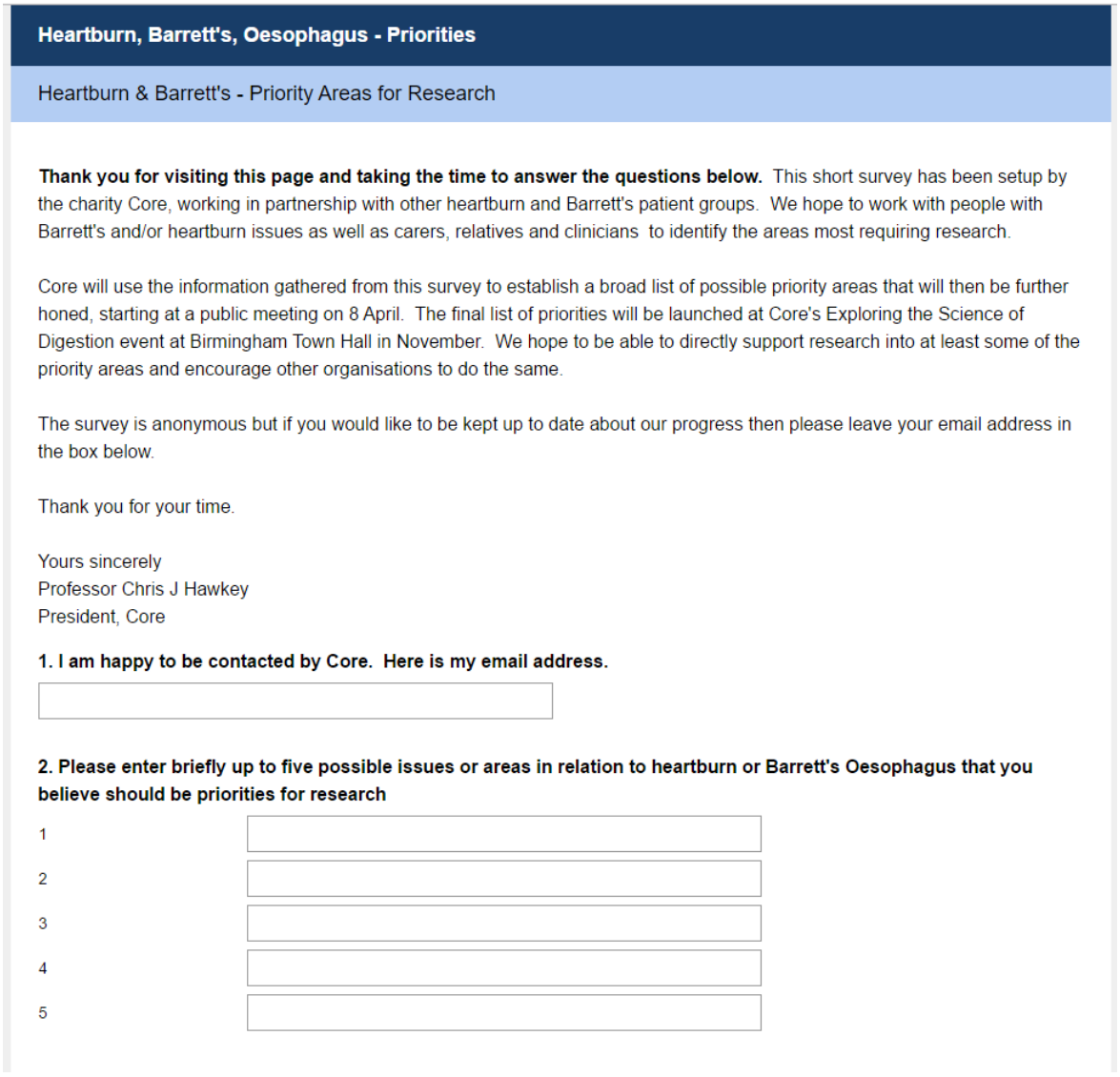
CWS Question*	4-point Likert scale	NDBO Percentage	DBO Percentage	GORD/dyspepsia Percentage	Colonic Polyp Percentage
1 How often have you thought about your chances of getting cancer?	Never	18.8% (56)	12.5% (6)	35.2% (45)	16.7% (24)
	Rarely	27.9% (83)	39.6% (19)	21.1% (27)	34.0% (49
	Sometimes	47.0% (140)	31.3% (15)	39.8% (51)	45.8% (66)
	Always	6.4% (19)	16.7% (8)	3.9% (5)	3.5% (5)
2 Have these thoughts affected your mood?	Never	43.6% (130)	45.8% (22)	49.2% (62)	49.3% (73)
	Rarely	27.2% (81)	22.9% (11)	20.6% (26)	27.7% (41)
	Sometimes	25.8% (77)	27.1% (13)	27.8% (35)	21.6% (32)
	Always	3.4% (10)	4.2% (2)	2.4% (3)	1.4% (2)
3 Have these thoughts interfered with your ability to do daily activities?	Never	72.4% (215)	68.8% (33)	73.8% (93)	79.2% (118)
	Rarely	16.2% (48)	12.5% (6)	11.9% (15)	14.8% (22)
	Sometimes	10.4% (31)	16.7% (8)	12.7% (16)	6.0% (9)
	Always	1.0% (3)	2.1% (1)	1.6% (2)	0.0% (0)
4 How concerned are you about getting cancer one day?	Never	18.1% (54)	17.0% (8)	28.8% (36)	17.4% (26)
	Rarely	32.2% (96)	29.8% (14)	29.6% (37)	33.6% (50)
	Sometimes	37.2% (111)	38.3% (18)	35.2% (44)	43.0% (64)
	Always	12.4% (37)	14.9% (7)	6.4% (8)	6.0% (9)
5 How often do you worry about developing cancer?	Never	24.2% (72)	18.8% (9)	34.9% (44)	27.7% (41)
	Rarely	34.3% (102)	35.4% (17)	31.7% (40)	35.8% (53)
	Sometimes	33.7% (100)	35.4% (17)	30.2% (38)	31.8% (47)
	Always	7.7% (23)	10.4% (5)	3.2% (4)	4.7% (7)
6 How much of a problem is this worry?	Never	37.2% (110)	41.7% (20)	47.6% (60)	43.0% (64)
	Rarely	33.4% (99)	37.5% (18)	27.0% (34)	37.6% (56)
	Sometimes	23.0% (68)	10.4% (5)	21.4% (27)	16.1% (24)
	Always	6.4% (19)	10.4% (5)	4.0% (5)	3.4% (5)

* Please note the question wording was adapted to relate specifically to each cohort cancer risk. For example, the BO cohort were asked in relation to oesophageal (gullet) cancer whereas the colonic polyp cohort were asked in relation to colorectal (bowel) cancer.

8.3. Chapter 4

8.3.1. Initial questionnaire

Figure 8.3.1-1 Research priority setting initial survey



Heartburn, Barrett's, Oesophagus - Priorities

Heartburn & Barrett's - Priority Areas for Research

Thank you for visiting this page and taking the time to answer the questions below. This short survey has been setup by the charity Core, working in partnership with other heartburn and Barrett's patient groups. We hope to work with people with Barrett's and/or heartburn issues as well as carers, relatives and clinicians to identify the areas most requiring research.

Core will use the information gathered from this survey to establish a broad list of possible priority areas that will then be further honed, starting at a public meeting on 8 April. The final list of priorities will be launched at Core's Exploring the Science of Digestion event at Birmingham Town Hall in November. We hope to be able to directly support research into at least some of the priority areas and encourage other organisations to do the same.

The survey is anonymous but if you would like to be kept up to date about our progress then please leave your email address in the box below.

Thank you for your time.

Yours sincerely
Professor Chris J Hawkey
President, Core

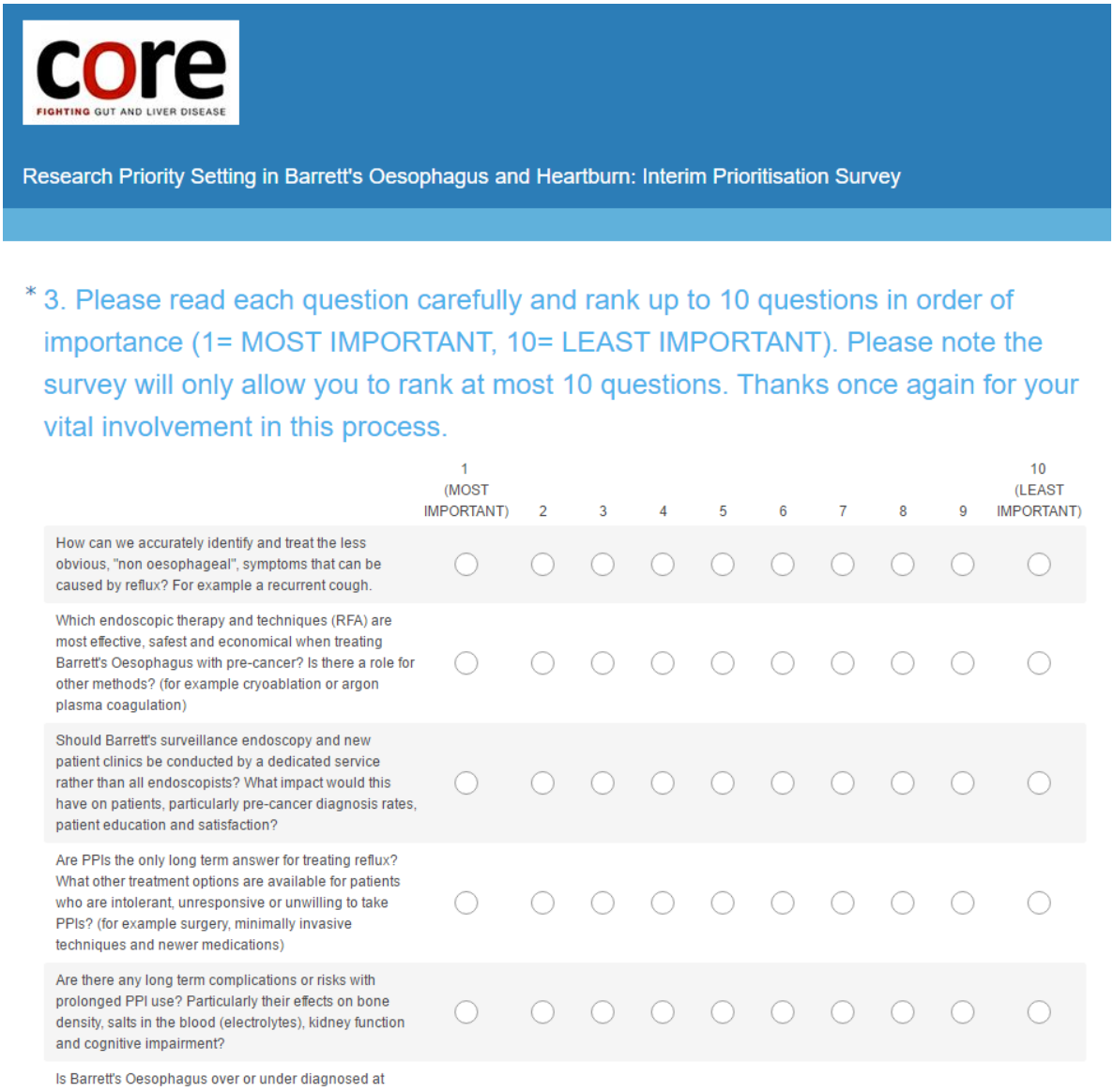
1. I am happy to be contacted by Core. Here is my email address.

2. Please enter briefly up to five possible issues or areas in relation to heartburn or Barrett's Oesophagus that you believe should be priorities for research

1
2
3
4
5

8.3.2. Interim priority setting questionnaire

Figure 8.3.2-1 Research priority setting interim prioritisation survey



core
FIGHTING GUT AND LIVER DISEASE

Research Priority Setting in Barrett's Oesophagus and Heartburn: Interim Prioritisation Survey

* 3. Please read each question carefully and rank up to 10 questions in order of importance (1= MOST IMPORTANT, 10= LEAST IMPORTANT). Please note the survey will only allow you to rank at most 10 questions. Thanks once again for your vital involvement in this process.

	1 (MOST IMPORTANT)	2	3	4	5	6	7	8	9	10 (LEAST IMPORTANT)
How can we accurately identify and treat the less obvious, "non oesophageal", symptoms that can be caused by reflux? For example a recurrent cough.	○	○	○	○	○	○	○	○	○	○
Which endoscopic therapy and techniques (RFA) are most effective, safest and economical when treating Barrett's Oesophagus with pre-cancer? Is there a role for other methods? (for example cryoablation or argon plasma coagulation)	○	○	○	○	○	○	○	○	○	○
Should Barrett's surveillance endoscopy and new patient clinics be conducted by a dedicated service rather than all endoscopists? What impact would this have on patients, particularly pre-cancer diagnosis rates, patient education and satisfaction?	○	○	○	○	○	○	○	○	○	○
Are PPIs the only long term answer for treating reflux? What other treatment options are available for patients who are intolerant, unresponsive or unwilling to take PPIs? (for example surgery, minimally invasive techniques and newer medications)	○	○	○	○	○	○	○	○	○	○
Are there any long term complications or risks with prolonged PPI use? Particularly their effects on bone density, salts in the blood (electrolytes), kidney function and cognitive impairment?	○	○	○	○	○	○	○	○	○	○
Is Barrett's Oesophagus over or under diagnosed at										

9. Supplementary CD-ROM Appendix

9.1. Chapter 2

9.1.1. Example of a fully coded thematic chart

9.1.2. Framework analysis concept map

9.1.3. Poster presentation: Barrett's oesophagus: a qualitative study of patient burden and follow up needs. BSG June 2018.

9.2. Chapter 3

9.2.1. Nearest neighbour matching analysis tables

9.2.2. Example of a participant cover letter

9.2.3. Example of a participant information sheet

9.2.4. Example of a participant questionnaire

9.3. Chapter 4

9.3.1. Associated presentations

- An Introduction to Research Priority Setting (project launch oral presentation at the 10th National Barrett's oesophagus symposium.
- Research Priority Setting Final Workshop (oral presentation)
- Dissemination of Results
    - Oral and poster presentation at The International Oesophageal Cancer Symposium
    - The Lancet (Gastroenterology and Hepatology) podcast feature for Research Priority Setting in BO and GORD.

9.4. Chapter 5

9.4.1. Poster presentation: A dedicated service improves the accuracy of Barrett's oesophagus surveillance: a prospective comparative