A core outcome set for clinical trials in oropharyngeal cancer

Thesis submitted in accordance with the requirements of the
University of Liverpool for the degree of Doctor in Philosophy

by

Aoife Máire Íde Waters

July 2017

Word count 74,436

Abstract for thesis

Author: Aoife Máire Íde Waters

Title: A Core Outcome Set for clinical trials in Oropharyngeal Cancer

The impact of randomized controlled trials is frequently diminished by disparate outcome reporting, precluding the comparison of results between trials or synthesis of data in meta-analyses. This is particularly problematic in lower incidence conditions such as Oropharyngeal squamous cell carcinoma (OPSCC), where the need to synthesise data from competing trials is greater. Minimum outcome reporting standards, known as Core Outcome Sets (COS) have been shown to increase the consistency of outcome reporting between trials of comparable interventions, thus facilitating the comparison or synthesis of trial data.

The objective of the work in this thesis was to identify outcomes of importance to patients, carers and healthcare professionals and define a COS for OPSCC. The methods used comprised a systematic review of OPSCC RCTs to identify the outcomes reported and establish whether there was outcomes heterogeneity as suggested by other studies; semi-structured qualitative interviews with patients and carers to establish their outcomes of importance; a Delphi Study of patients, carers and healthcare professionals, to reach consensus on the outcomes that should be included in a COS for OPSCC.

The systematic review described in chapter two identified significant heterogeneity in outcome reporting; 58 outcomes were reported in 43 RCTs, only three outcomes were measured in more than 50% of studies, and only 41% of outcomes were measured in more than one study. The qualitative study identified 136 outcomes. Survival and late adverse effects of treatment are of greatest priority to patients and carers. The Delphi study successfully reached consensus on eight outcomes for inclusion in the COS.

There is substantial heterogeneity in the outcomes measured in contemporary RCTs in OPSCC. Yet, there is strong consensus between stakeholder groups in the outcomes of importance. Implementation of the COS will increase the consistency of outcome reporting thus facilitating the comparison of data from competing trials and synthesis of data in meta-analyses.

Further consideration must be given to ways in which the uptake of COS can be maximised to have the highest impact. The COS is applicable to trials of interventions used in current clinical practice, however the advent of new treatment strategies may require that this is reviewed and adapted.

Statement of contribution

Conception and study design	Dr Aoife M I Waters Professor Terry M Jones Professor Catrin Tudur Smith Professor Bridget Young
Critical revision and approval of final manuscript	Dr Aoife M I Waters Professor Terry M Jones Professor Catrin Tudur Smith Professor Bridget Young

Samantha Faulkner (Cochrane) provided the original search strategy for the systematic review described in chapter two and guidance on its modification for use in other databases.

Lisa Williamson (University of Liverpool) and Kate Lightbody (Aintree University Hospital NHS Foundation Trust) were second reviewers for the systematic review presented in chapter two. They were involved in screening records and checking for correct exclusion of studies.

Ethics Statement

Ethical approval for this study was granted in the UK by the Liverpool Central Research Ethics Committee (reference 12/NW/0708). The study was registered on the NIHR portfolio, ID 13823 (17 January 2013).

Approval at MDACC (Houston, TX, US) was provided by the Institutional Review Board (IRB) (protocol number 2013-0285).

Acknowledgements

First and foremost, I offer my sincerest gratitude to my supervisors, Professors Terry Jones, Catrin Tudur-Smith and Bridget Young, for their patience, guidance and unwavering support, in many an hour of self-doubt.

I would have been unable to complete this thesis without the support of Andrew Robson and my clinical colleagues in Carlisle and Newcastle, to whom I am deeply indebted.

I thank Martha Portwood, Shirley Pringle and my collaborators, Professor Kate Hutcheson and Dr Jo Patterson for the tremendous amount of time and effort contributed in identifying and recruiting participants, and for being truly inspirational women, clinicians and academics.

I reserve deep gratitude to the patients and carers, without whom this endeavour would not have been possible. I hope that the influences of this research are far-reaching. I would also like to thank the healthcare professionals involved and for Mererid Evans for allowing me to hijack the PATHOS investigator meeting to rally recruits.

For my funding, I thank the MRC North West Hub for Trials Methodology Research and the British Association of Head and Neck Oncologists and The Royal Society of Medicine for travel grants to fund my research trip to Houston.

However, I reserve my most heartfelt thanks for my family. My parents, for their constant love and support and for believing in me wholeheartedly. My husband, Ron, who has made uncountable sacrifices to help me balance clinical, academic and home life, and whose bravery, integrity and resilience are a constant source of inspiration. I dedicate this thesis to him and to my darling daughter Ruby, who brings me sheer joy, every day. She has not known life without this thesis, and so I hope one day this makes her proud, and that she too realises, no matter the obstacles along the way, you can do anything if you put your mind to it.

Abbreviations

ANCOVA	Analysis of Co-Variance
BOT	Base of Tongue
CENTRAL	Cochrane Central Register of Controlled Trials
COMET	Core Outcome Measures in Effectiveness Trials
CONSENSUS	Squamous Cell Carcinoma of the Oropharynx: Late Phase Clinical Trial Core Outcomes
COREQ	Consolidated Criteria for Reporting Qualitative Studies
COS	Core Outcome Set
COS-STAR	Core Outcome Set-STAndards for Reporting
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
CRT	Chemoradiotherapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
FDA	Food and Drug Administration
GORTEC	Multicentre Hellenic Cooperative Oncology Group
GP	Glossopharyngeal Sulcus
HR-QOL	Health-Related Quality of Life
HPV	Human Papillomavirus
ICF	International Classification of Functioning, Disability and Health
ID	Identification
IMD	Index of Multiple Deprivation
IMRT	Intensity-Modulated Radiation Therapy

IQR	Inter-quartile range
IRB	Institutional Review Board
LENT-SOMA	Late Effects of Normal Tissues Subjective-Objective Management Analytic
MDACC	MD Anderson Cancer Center
MOMENT	Management of Otitis Media with Effusion in Cleft Palate
MRND	Modified Radical Neck Dissection
NCRI	National Cancer Research Institute
NG	Nasogastric
ND	Neck Dissection
NHS	National Health Service
NIHR	National Institute for Health Research
OMI	Outcome Measurement Instrument
OMERACT	Outcome Measures in Rheumatology
OPSCC	Oropharyngeal Squamous Cell Carcinoma
ORL-HNS	Otorhinolaryngology-Head and Neck Surgery
PEG	Percutaneous Endoscopic Gastrostomy
PoPPIE	People and Patient Participation, Involvement and Engagement
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient Reported Outcome Measure
QI	Qualitative Interviews
RCT	Randomized Controlled Trials
R&D	Research and Development
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SCCHN	Squamous Cell Carcinoma Head and Neck
SWOG	Southwest Oncology Group
SR	Systematic Review
SRQR	Standards for Reporting Qualitative Research
TLM	Transoral laser microsurgery
TORS	Transoral robotic surgery
TROG	Trans-Tasman Radiation Oncology Group
TX	Texas

Initials of researchers involved in thesis research

AW	Aoife M I Waters
BY	Bridget Young
CTS	Catrin Tudur-Smith
JMP	Joanne M Patterson
KAH	Katherine A Hutcheson
KL	Kathryn Lightbody
LW	Lisa Williams
MHJ	Melanie Harper-Jones
TMJ	Terry M Jones

Table of Contents

List of tables and figures

Tables

Figures

Boxes for qualitative quotes

Publications

Waters AMI, S. C., Young B, Jones TM (2014). "The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer." Trials **15**(168).

Chapter 1
Introduction and background

1.1 Squamous cell carcinoma of the head and Neck

Head and Neck Squamous cell carcinomas (SCCHN) are a biologically diverse group of cancers affecting the mucosal surfaces of the upper aero-digestive tract. Sub-sites include the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx [1, 2]. For individual sub-sites, the incidence of these cancers is relatively low, however, as a group, SCCHN is the sixth most incident cancer worldwide [3].

Loco-regional spread to the cervical lymph nodes at presentation is common, and associated with a poorer prognosis. Patients with distant metastatic spread are generally treated in a palliative capacity. Those with disease recurrence have a poor prognosis and the treatment options depend largely on the treatment already received for the primary tumour. The median survival of patients with recurrent or metastatic SCCHN in most series' is six to nine months depending upon patient and disease-related factors [4].

Treatment of SCCHN relies on radiotherapy (RT), surgery +/- post-operative RT or cisplatin based chemoradiotherapy (CRT), CRT alone or following induction chemotherapy. Multimodality treatment is usually required for disease control and, increasingly, small molecule adjuvants are now being used [5].

The complex anatomy and functions of the upper aero-digestive tract mean that radical treatment to this area is associated with variable, but often significant and complex functional deficits. Speech and swallowing are predominantly affected but aesthetic changes are also a concern for many patients and consequently, treatment

can have a profound effect on a person's quality of life, social interactions, relationships and employment [6].

There are significant geographical variations in the incidence and primary site of SCCHN, likely reflecting the prevalence of known risk factors as well as genetic and ethnic predisposition amongst populations [4]. In the developed world, tobacco smoking and alcohol consumption are the most important risk factors, which often act synergistically, and, by repeated exposure, causing "field cancerization" in the mucosa of upper aero-digestive tract [1]. There is a dose-response relationship; with a higher relative risk of developing SCCHN in longer-term smokers. This declines upon cessation of smoking [7, 8]. Persistent smoking increases the risk of early and late adverse effects of treatment and compromises long-term disease control and overall survival [9]. A decrease in the incidence of laryngeal SCC has correlated with a reduction in the prevalence of tobacco smoking, yet in the oropharynx subsite, SCC is increasing [10].

SCCHN is more common in socio-economically disadvantaged groups [11-13]. This has been attributed to increased consumption of tobacco and alcohol in patients with lower socio-economic status (SES) [11], however other theories include exposure to toxic chemicals [14], increased exposure to human papillomavirus (HPV) [15], differences in diet [16-18] and poorer oral hygiene [19]. Lower SES is also associated with poorer outcomes [20-23]. Data from the United States have shown that those without private medical insurance are at increased risk of death after a diagnosis of SCCHN when compared with patients with private insurance, after adjustment for age, gender, race, smoking, alcohol use, site, socioeconomic status, treatment, and cancer stage [24]. Psychosocial support is extremely important in patients going through treatment for SCCHN. A 2013 analysis of SEER (Surveillance, Epidemiology and End Results) data by Aizer et al. [25] of 1,260,898 patients diagnosed with lung, colorectal, breast, pancreatic, prostate, liver/intrahepatic bile duct, non-Hodgkin lymphoma, head and

neck, ovarian and oesophageal cancer showed that married patients were less likely to present with metastatic disease (adjusted odds ratio [OR], 0.83; 95% CI, 0.82 to 0.84; $P < .001$), more likely to receive definitive therapy (adjusted OR, 1.53; 95% CI, 1.51 to 1.56; $P < .001$), and less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79 to 0.81; $P < .001$) than unmarried patients. These associations remained significant when each individual cancer was analyzed ($P < .05$ for all end points for each malignancy), however married patients with head and neck cancers displayed the greatest relative reduction in cancer death (33%). For a number of cancer sites including head and neck, the survival benefit associated with marriage was larger than the published survival benefit of chemotherapy. There are likely to be many reasons for this effect; married patients are more likely to have better access to healthcare [26], marital status may also impact stage at diagnosis as patients with a spouse may be encouraged to seek medical attention for worrisome symptoms [25], spouses may also encourage patients to undergo definitive versus expectant management [27]. Psychosocial support allows patients to share the emotional burden of a cancer diagnosis. Patients who are married display less distress, depression and anxiety [28]. The spouse, family members and/or close friends often play a central role in the care of the patient with OPSCC. The morbidity associated with radical multi-modality therapy means that patients are often unable to carry out many of their normal activities and require assistance with some of the most basic functions including self-care and meal preparation. Those close to the patient are often the ones to seek medical assistance on behalf of the patient if required. Probably the most significant reason for marital status conferring survival advantage is that married patients have better adherence with prescribed treatments [29] and in SCCHN missed or delayed radiation treatment is associated with increased rates of loco-regional recurrence and death [30].

1.2 Oropharyngeal squamous cell carcinoma

National cancer registries in the United Kingdom have recorded a doubling in the incidence of Oropharyngeal Squamous Cell Carcinoma (OPSCC) over the last decade, and this trend is mirrored in Northern Europe, the USA and Australasia [31-35]. Oncogenic human papillomavirus genotype 16 (HPV-16), has been attributed as the cause for this increase in incidence worldwide, with the National Cancer Institute in the US estimating a 225% increase in HPV-positive OPSCC between 1988 and 2004, and a 50% reduction in the incidence of HPV-negative OPSCC [36].

It seems that the attractive proposition of an epidemic caused by a single aetiological agent may not be so simple. A recently published multicentre cross-sectional retrospective study of archival tumour tissue blocks, aimed at determining the proportion of HPV-positive and HPV-negative OPSCC in the United Kingdom between 2002 and 2011, has shown that the proportion of HPV-positive cases remained static, at around 50%, whilst the overall incidence of OPSCC doubled [37]. These results suggest that the rapidly increasing incidence of OPSCC in the UK cannot be solely attributed to the influence of HPV. In addition to smoking and alcohol consumption, HPV remains an important risk factor for OPSCC, although exposure to risk factors and their significance seems to vary by population. In the Netherlands, a nationwide study comprising all 16,480 patients with oral tongue SCC (OTSCC), oral cavity SCC (OCSCC) excluding tongue and OPSCC, demonstrated similar increases in the incidence of OCSCC and OTSCC as for OPSCC [38]. This does not support the assumption that HPV is the main contributor to a rising incidence of OPSCC and tobacco and alcohol remain important risk factors. Furthermore, Dutch molecular epidemiological evidence of HPV DNA positive OPSCC, documented a HPV-positive incidence around 30-40% over the last decade 26-28 [39-41].

HPV-positive OPSCC occurs in a younger patient cohort than HPV-negative disease and confers substantial benefits in terms of survival, with a 58% reduction in the risk of death demonstrated by Ang et al. in their analysis of RTOG 0129 RCT [42-45]. Whilst these patients can be reassured of a five-year survival likelihood of greater than 80%, the functional deficits associated with multi-modality therapy remain substantial [2, 44]. Patients will live longer with the side-effects of treatment, which are potentially more debilitating, and less acceptable to those with young families, long lives and careers ahead of them.

It is likely that the outcomes prioritised by this new cohort of younger, more educated patients will differ from older patients with SCCHN related to tobacco and alcohol consumption. Prior to the advent of HPV related OPSCC, research conducted to establish outcome priorities in SCCHN patients showed that these differ between patients of different age groups, and naturally amongst individuals with different priorities and expectations. In a study by List et al. in which patients with SCCHN were asked to rank outcomes of importance prior to starting treatment, pain was a greater priority than cure in older patients compared with younger patients [46]. A systematic review published in 2016 which sought to establish outcome priorities for head and neck cancer patients could make no conclusions about the outcome priorities of OPSCC patients due to significant heterogeneity between studies and called for research to establish outcome priorities in patients with HPV-positive disease [47].

Despite the introduction of new therapeutic strategies, the five-year overall survival for HPV-negative cancer has remained at approximately 50-60% over the last three decades [45, 48]. So whilst clinical trials in HPV-positive OPSCC may seek to prioritise functional outcomes, a drive to improve survival remains the focus in HPV-negative disease.

1.2.1 Treatment strategies

Historically, the treatment of choice for locally advanced OPSCC was open surgical resection involving mandibulotomy and reconstruction followed by conventional radiotherapy. The surgery, a major undertaking for both the patient and medical team, was often associated with significant short and long-term dysfunction in speech and swallowing, higher levels of severe complications and unacceptable cosmetic defects [49]. In the 1970s and 1980s a number of adverse pathological features associated with an increased risk of loco-regional recurrence following surgery for SCCHN were identified. These included inadequacy of surgical margins around the primary tumour, primary tumour site, advanced T-stage, perineural invasion, lymphovascular invasion, number and location of malignant neck nodes and extracapsular spread [50-54]. The RTOG 73-03 trial demonstrated the benefits of post-operative radiotherapy in terms of loco-regional control [55]. A subsequent SEER population-based analysis demonstrated a survival gain of 10% in patients with adverse pathological features receiving adjuvant radiotherapy [56]. In 2005, a pooled analysis of two RCTs from the RTOG and EORTC which compared adjuvant post-operative radiotherapy (PORT) versus post-operative chemoradiotherapy (POCRT) showed a significantly improved survival in patients some adverse pathological features. On the basis of this data, POCRT became standard of care for the adjuvant treatment of patients with SCCHN with these high-risk pathological features. The majority of patients are categorised into this group. Open surgery therefore fell out of use in favour of ‘organ-sparing’ cisplatin-based chemoradiotherapy regimens [57, 58], the benefits of which, over radiotherapy alone, were further demonstrated in the seminal MACH meta-analysis [59]. Whilst these regimens are widely considered to be the current standard of care for patients with locally advanced OPSCC, they have never been directly compared with surgical techniques in a randomized controlled trial [60], and a growing body of evidence suggests that long-term swallowing function is not necessarily optimised by this choice of treatment strategy [61-64].

The incidence of severe acute toxicity doubles with the addition of chemotherapy, this includes treatment related deaths. Higher rates of severe late toxicity are also seen compared to PORT alone [65, 66].

Advances in minimally invasive surgical techniques with the use of transoral laser or robotic resection have challenged the status quo, with evidence suggesting that functional outcomes are superior, without compromise in oncological outcomes [67-69].

The changing aetiology of the disease, improvements to survival and functional expectations of patients naturally drive us to question the appropriateness of contemporary, radical treatment strategies, and whether de-escalation may achieve similar survival outcomes but lower the incidence and severity of post-treatment functional deficits. In the UK alone, a number of trials are under way to investigate whether such de-escalation is possible. De-ESCALaTE HPV (**De**termination of **E**pidermal growth factor receptor inhibitor (cetuximab) versus **S**tandard **C**hemotherapy (cisplatin) early **A**nd **L**ate **T**oxicity **E**vents in **H**uman **P**apilloma**v**irus positive oropharyngeal squamous cell carcinoma, NCT01874171) compares radiotherapy concomitant cetuximab, an epidermal growth factor receptor inhibitor, or cisplatin in patients with low-risk HPV-positive OPSCC with toxicity as the primary outcome. The primary outcome of PATHOS (Post-operative Adjuvant Treatment for HPV-positive Tumours, NCT02215265) is patient reported swallowing, measured using the MD Anderson Dysphagia Inventory.

The likelihood is that patient stratification and refinement of study populations in OPSCC clinical trials based on social, demographic and tumour characteristics will continue. The RTOG 0522 trial comparing radiotherapy and cisplatin plus or minus cetuximab showed no significant difference in progression-free survival, overall survival, loco-regional failure or distant metastasis between the treatment arms,

and so these were combined for the correlative analysis. This identified more than 10 pack-years of cigarette smoking as an independent predictor of poor prognosis; other predictors were p16-negative carcinoma, N2b-3 category, T4 tumour, and poor performance status. The authors supported a strategy of designing future trials for better biologically defined HNC entities. This means, however, that the number of patients eligible for a given trial will decrease progressively. To overcome this problem, Ang et al. encourage international collaborations to complete patient accrual in a timely fashion [70].

Large multi-centre trials are often complex, expensive and require significant time for adequate recruitment, which is often not reached. Registry based RCTs (RRCT) have been proposed as an alternative methodological approach to increase the efficiency and cost-effectiveness of clinical trials [71]. Large-scale clinical registries initiated to assess the quality of clinical performance are, at present, successfully collecting data from consecutive patients in many hospitals and health-care organizations; Denmark, Sweden, and the UK have some of the most complete national databases [72]. Patients can then be randomly allocated with most of their required baseline medical history already recorded, minimizing the need for additional data collection and onsite monitoring. This concept is the foundation for the design of registry-based randomized trials, which may be a possibility in the future in SCCHN [73].

There is significant variation in the incidence and severity of post-treatment functional deficits in OPSCC patients, in addition to relatively small numbers, tumour biological heterogeneity and variable response to treatment. As such these cancers pose particular challenges to researchers when selecting which outcomes to measure in trials. However, with individualised therapies becoming more of the norm, and therefore the numbers of comparable patients/interventions decreasing there is an urgent need to ensure that results can be compared between trials and synthesised in meta-analyses. Currently, no outcome reporting standard exists for clinical trials in OPSCC to ensure that this happens [74].

1.3 Clinical trials in healthcare

Clinical trials are research studies undertaken for the purpose of assessing the safety and efficacy of interventions, treatments or care procedures. Early phase clinical trials are often conducted to establish the safety or efficacy of a particular intervention and are carried out in a small number of participants. Such efficacy or explanatory trials determine whether an intervention can have a beneficial effect in an ideal situation under optimum conditions [75]. These tend to precede effectiveness trials (or pragmatic trials), which measure the degree of beneficial effect under 'real-world' clinical settings, conducted following as close to clinical practice as possible [76].

Clinical trials establish the efficacy or effectiveness of an intervention by comparing its beneficial and harmful effects on a number of pre-determined outcomes (the outcome variables or endpoints). The selection of the most important outcomes is therefore essential if research is to inform the evidence base for a particular clinical condition or intervention and ultimately influence clinical practice. Clinical trial data is used to inform clinical guidelines and shared decision making practices and in the development of health policies such as those by The National Institute for Health and Clinical Excellence (NICE) [77].

Randomized controlled trials (RCTs) are seen as the gold standard for evaluating the effects of treatments because they employ more robust methodological standards for assessing the effectiveness of interventions in healthcare [78]. RCTs used randomised treatment allocation to prevent selection bias by distributing the characteristics of patients that may influence assessment of treatment between groups [79]. RCTs eliminate selection bias by balancing both known and unknown prognostic factors, in the assignment of treatments [80]. Without randomisation, treatment comparisons may be prejudiced, whether consciously or not, by the

selection of participants of a particular kind to receive a particular treatment. Random assignment permits the use of probability theory to express the likelihood that any difference in outcome between intervention groups merely reflects chance [81]. The final advantage of random allocation is that in some situations it facilitates blinding the identity of treatments to the investigators, participants, and evaluators which reduces bias after assignment of treatments [82]. Of these three advantages, reducing selection bias at trial entry is usually the most important [83].

In addition to the a priori selection, consistent definition, measurement and reporting of outcomes, to provide unbiased estimates of treatment effect, trials must follow a predetermined protocol that describes the patients, an appropriate method for random allocation, follow up procedures and the statistical methods that will be used [84, 85]. As such, the choice of outcomes in clinical trials is an important design consideration.

1.3.1 Primary and secondary outcomes

Generally, there should be only one primary outcome, and a limited number of secondary outcomes in a clinical trial [85]. The greater the number of outcomes, the greater the number of tests undertaken, raising the probability of finding a statistically significant result by chance alone [86]. Additionally, this places a greater burden on the patients under investigation and the available resources. Clinical trials frequently measure more than one primary outcome, either because it is unclear which outcome will best answer the research hypothesis or where they are thought to be of equal importance. Outcomes may also be added during the course of a trial or may not be reported having been pre-specified in the protocol. When Smyth et al. interviewed trial investigators, the reasons for omitting pre-specified outcomes related to data collection being too expensive or complicated, as well as there being insufficient time and resources to collect less important secondary outcomes [87]. Reasons given for the addition of outcomes were

associated with poor research practice and were attributed to shortfalls in the writing of the protocol.

The primary outcome of a study should be that which is capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy [85]. Effectiveness trials (pragmatic trials) measure the degree of beneficial effect under "real world" clinical settings, and the design of an effectiveness trial is therefore formulated based on conditions of routine clinical practice and on outcomes essential for clinical decisions [88].

Secondary outcomes evaluate other beneficial or harmful effects of an intervention. These may be specific to only some comparisons in the review. For example, laboratory tests and other surrogate measures may not be considered as main outcomes as they are less important than clinical endpoints in informing decisions, but they may be helpful in explaining effect or determining intervention integrity [89].

1.3.2 Types of outcomes

Outcomes can relate to the effect of an intervention on key clinical indices, such as survival or disease control; they can also relate to surrogate markers such as laboratory tests or physical signs, used as a substitute to a clinical outcome [90]. The theoretical advantage of surrogate outcomes is that they may be able to predict the benefit of an intervention in advance of clinical outcomes, allowing for smaller recruitment to trials or shorter follow-up time. Where urgency dictates, such as in cancers with few therapeutic options, surrogate outcomes may allow for interventions to be made available to patients more quickly [90]. They are commonly employed in clinical trials but many criticisms have been levelled at

their use [91-93]. Systematic reviews of oncology clinical trials suggest that the strength of association between surrogate endpoints and life extension is generally low [94, 95]. Furthermore, drug approvals based on surrogate outcomes are frequently not followed up with prove of benefit on outcomes such as survival and quality of life. In a retrospective cohort study, Davis et al. analysed EMA oncology drug approvals 2009 – 13 to determine the availability of data on overall survival, the gold standard primary outcome for oncology trials, and quality of life benefits of cancer drugs approved in Europe [96]. This showed that most drugs enter the market without evidence of benefit on survival or quality of life, and with a median of 5.4 years' follow up, only 51% were associated with significant improvement in survival or quality of life.

Its reliability, straightforward interpretation and clinical usefulness make overall survival the gold standard endpoint to measure the effect of treatment in SCCHN [97]. Detecting statistically significant differences in this outcomes requires a large number of patients and an extended follow-up period and surrogate endpoints are therefore commonly employed. The strength of association between these surrogate outcomes and overall survival is variable. Loco-regional control and event-free survival have been shown to have a strong association with overall survival. In 116 treatment comparisons for 22,744 patients Michiels et al. showed that for radiotherapy treatment, effects on both duration of loco-regional control and event-free survival were strongly correlated with those on overall survival. For chemotherapy, correlation coefficients between treatment effects on event-free survival and overall survival were larger than those between duration of loco-regional and overall survival [97]. Response rate is rigidly defined by criteria for tumour shrinkage [98, 99] and frequently used to assess the benefit of systemic chemotherapy. An initial response to treatment with chemotherapy is common in SCCHN, yet this outcome has been consistently shown to have little association with survival benefit in studies of SCCHN [100, 101]. In gaining accelerated approvals, the U.S. FDA deem that surrogate endpoints may be acceptable, with a

sponsor commitment to provide evidence of clinical benefit in a subsequent trial [102]. Furthermore, close attention must be paid to reduce the risk of bias when using such outcomes; blinding of both patients and investigators to treatment assignment may be necessary. In the last couple of decades, accumulating research has sought to establish the best methods for validating surrogate outcomes. Whilst no consensus exists regarding the standards needed to identify valid surrogates, correlation and meta-analytic approaches are the most widely accepted methods [103, 104]. The use of surrogate outcomes must be carefully considered, and only those chosen for which there is strong evidence of an association with longer term outcomes such as survival and quality of life. Where survival between treatment arms is equivalent, or there is an assumption of equivalence, outcomes other than overall survival may take precedence. This approach has been used in trials of laryngeal preservation [105-107] and HPV-positive OPSCC [108].

Smaller sample sizes, and/or shorter follow up are also permitted by the use of composite outcomes, thereby improving statistical efficiency in time to event trials [84]. Composite outcomes, in which multiple endpoints are combined, are frequently used in clinical trials that are expected to have an effect on mortality and major morbidity. However, methodological issues are often associated with their use, as identified in a systematic review by Cordoba et al. who found that trials with composite outcomes were often problematic, 'characterised by a lack of logic behind the construction of the composites, inconsistent and unclear reporting, post hoc changes to the composites, and cherry picking' [109]. A substantive risk associated with the reporting of composite outcomes is that the benefits described may be presumed to relate to all of the components [84]. A relationship must exist between the variables of the composite outcome such that they can sensibly be added together as being aspects of the same underlying disease process. Ferreira-González et al [110] make 3 recommendations for use of composite outcomes: they should include components that are similar in importance to patients, that occur with similar frequency, and that are affected to a similar degree by the intervention.

Composite outcomes are frequently employed in clinical trials in SCCHN. Loco-regional control refers to disease control at the primary site and in the cervical lymph nodes; an event may therefore comprise either local or regional disease recurrence. The use of this outcome is further complicated by inconsistent definitions across the trials using it. In a large systematic review of SCCHN randomized trials published in 2009, Le Tourneau et al showed that loco-regional control and overall survival account for 70% of primary endpoints, yet, among 72 endpoints tracking loco-regional failures 29% did not define the term and 64% specified the absence of complete response as a failure [111]. As previously mentioned, event-free survival is a surrogate outcome shown to have a strong association with overall survival in SCCHN trials. In their paper suggesting that event-free survival is a more suitable surrogate outcome for SCCHN trials than loco-regional control Michiels et al. also noted heterogeneity between trials in the definition of these outcomes. They chose to define event-free survival as the time from randomisation to the first event of either loco-regional or distant recurrence or death from any cause. This outcome, defined as such, was often called disease-free survival in trials that included patients with resectable tumours and progression-free survival in trial that included patients with non-resectable tumours [97].

Patient reported outcomes (PRO) measure how a patient feels or functions and are collected directly from the patient without interpretation by anyone else [112]. PROs may measure health-related quality of life (HR-QOL), symptoms, satisfaction or adherence to medication and help to evaluate the burden of disease and treatment from the patients' perspective [113]. They are often collected using measurement tools (PROMs) that assess the patient's view of their symptoms, functional status or quality of life [114]. The measurement of PROs in clinical trials has increased substantially in the last 20 years [115]. The same considerations must apply to the measurement of PROs in trials as for other outcomes, as their inappropriate use or lack of transparency in their measurement or reporting could compromise the quality of trial data. With some of these

concerns in mind, the CONSORT (Consolidated Standards of Reporting Trials) group, whose guidance facilitates the transparent and robust reporting of RCTs, published a PRO extension to their guidance that aims to improve the reporting of PROs in trials to facilitate the use of results in informing clinical practice and health policy [116]. CONSORT is discussed in more detail later in this chapter. Many PROMS are available in oncology, several with SCCHN specific extensions. There are also PROMS designed for SCCHN specifically, and to measure patient symptoms of specific sequelae of treatment.

1.3.3 Outcome domains

Outcome domains are constructs used to classify broad aspects of the effects of interventions e.g. functional status. In the context of clinical trials, outcomes from multiple domains or multiple outcomes within a domain may be important to measure [117].

1.3.3.1 Outcome-related frameworks

Outcome domain models for frameworks exist to provide essential structure to the conceptualisation of domains, however in a review of Health Related Quality of Life (HRQOL) models, Bakas et al. found that there were wide variations in terminology for analogous HRQOL concepts [118]. Some of the frameworks to classify health, disease and outcomes are described below.

World Health Organisation (WHO)

The WHO is responsible for developing a number of frameworks related to health outcomes. In 1948, the WHO defined health as a construct comprising three domains: physical, mental and social wellbeing [119]. They do not however specify what should be included within each of these domains [120] and this

definition is considered out of date by some given the rise in chronic diseases [121].

The International Classification of Functioning, Disability and Health (ICF), endorsed by WHO (member states) in 2001, provides a framework for classifying health and health-related domains for measuring health and disability at both individual and population levels. This was developed as a globally accepted framework and classification system based on a bio-psycho-social model to assess and compare functional outcomes [122]. The ICF-classification contains more than 1,400 categories. To make these applicable to every-day clinical practice, ICF core sets have been established. The ICF core set for head and neck cancer serve as minimal standards for the assessment and documentation of functioning and health of persons with SCCHN in clinical studies, clinical encounters and multi-professional comprehensive assessment. Although the ICF is widely comprehensive, it is not all inclusive. For example, the ICF does not include outcomes such as death, an outcome that is especially important to measure in clinical trials investigating treatments for life threatening illnesses such as cancer. Furthermore is has not been widely adopted and is not used by cancer registries.

Patient-reported Outcomes Measurement Information System (PROMIS)

PROMIS (Patient-Reported Outcomes Measurement Information System) is a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children [123]. It can be used with the general population and with individuals living with chronic conditions. The PROMIS domain framework builds on the WHO definition of health to provide subordinate domains beneath the broad headings in the definition of health: physical (symptoms and functions), mental (affect, behaviour and cognition) and social wellbeing (relationships and function).

5Ds

This framework for representing patient outcomes was developed specifically for rheumatic diseases and is presented as a systematic structure for representation of patient outcomes including five dimensions: death, discomfort, disability, drug or therapeutic toxicity and dollar cost [124].

Wilson and Cleary

Wilson and Cleary propose a taxonomy for different measures of health outcomes and specific causal relationships between them that link traditional clinical outcomes to measures of health-related quality of life [125].

The Outcome measures in rheumatology (OMERACT) Filter 2.0

The OMERACT Filter 2.0 is a conceptual framework for the measurement of health conditions in the setting of interventions comprising three core areas: death, life and impact and pathophysiological manifestations [120]. A measurement of resource use is also strongly recommended. They recommend that the ICF domains are also considered under life impact (ICF domains: activity and participation) and pathophysiological manifestations (ICF domains: body function and structure). OMERACT recommends the inclusion of at least one outcome reflecting each core area in COS, however this may not always be appropriate [126].

Outcome Measures Framework (OMF)

This project was funded by the Agency for Healthcare Research and Quality (a branch of the U.S. Department of Health and Human Services) to create a conceptual framework for development of standard outcome measures used in patient registries [127]. This comprises three broad domains: characteristics, treatments and outcomes, with six subcategories within the outcome domains: survival, disease response, events of interest, patient/caregiver-reported outcomes, clinicians-reported outcomes and health system utilisation.

Survey of Cochrane reviews

Cochrane reviews were analysed by Smith et al. to identify whether similar outcomes were measured across different disease categories [128]. Fifteen categories of outcomes were prominent across Cochrane review groups: adverse events of effects, mortality/survival, infection, pain, other physiological or clinical psychosocial, quality of life, activities of daily living, medication, economic, hospital, operative, compliance (with treatment), withdrawal (from treatment or study) and satisfaction (patient, clinician, or other health care provider).

1.3.4 Outcome selection in clinical trials

The outcomes measured will depend on the clinical condition, the research question and the intervention being assessed. Trialists must bear in mind the clinical relevance of an outcome, whether it is responsive to the interventions being compared, how it is assessed, and whether it is appropriate and practicable given the time and financial constraints of the trial and the nature of the clinical condition.

The heterogeneity of outcome reporting in clinical trials is a significant barrier to the synthesis of individual trial data. Meta-analyses are frequently unable to make firm conclusions about the effectiveness of interventions because comparable trials don't use comparable outcomes, or define or measure them in the same way. The five most accessed Cochrane reviews in 2009, together with the top cited review in that year, all described inconsistencies in the outcomes reported in eligible trials and a call for the standardization of outcomes is a regular conclusion of systematic reviews [129]. Clinical guidelines and recommendations are based on this evidence and otherwise well conducted trials may have little to contribute to this evidence base if the outcomes reported are inconsistent with those in comparable trials. Research findings may also have little application in the real world if the outcomes reported are not clinically relevant or are of little value to patients. Consistent

outcome selection in trials in a particular clinical area has the potential to improve the quality of research by allowing for results between trials to be more easily compared and combined [130]. Kirkham et al. demonstrated an increase in the consistency of outcome measurement in clinical trials in rheumatoid arthritis (RA) in the years following the publication of the RA COS [131].

1.3.4.1 The effect of bias in outcome selection and reporting

Well-designed randomized controlled trials will specify the outcomes to be measured in their study protocol and adhere to reporting these irrespective of the results. The failure to report all pre-specified outcomes in a clinical trial can introduce a type of bias known as outcome reporting bias (ORB). This is the selective reporting or 'cherry-picking' of the outcomes to be reported from those measured in the course of a trial, because of the results [132]. This kind of bias affects not just the interpretation of the individual trial but also any subsequent systematic review of the evidence base that includes it [133] and raises serious questions about the legitimacy of the research and possibly the integrity of the researchers [87].

In a review by Kirkham et al. investigating ORB in an unselected cohort of 283 Cochrane reviews, more than half of the reviews did not include full data for the review primary outcome of interest from all eligible trials [134]. Of the 42 meta-analyses with a statistically significant result only, eight (19%) became non-significant after adjustment for outcome reporting bias and 11 (26%) would have overestimated the treatment effect by 20% or more. This study is likely to underestimate the effect of outcome reporting bias because it looked only at primary outcomes. Secondary outcomes are more likely to be changed than primary outcomes as they are usually of less clinical importance.

In a related study, Smyth et al. conducted a systematic review and series of interviews with trialists to establish the frequency of and reasons for ORB [87]. The prevalence of incomplete outcome reporting was high, and trialists seemed generally unaware of the implications for the evidence base of not reporting all outcomes. A general lack of consensus regarding the choice of outcomes in particular clinical settings was evident and this had an impact upon trial design, conduct, analysis, and reporting. Issues such as missing data, delays in data collection and concerns about the validity of trial results render study outcomes more likely to remain unreported [87]. Chan et al. have suggested this may arise because researchers did not feel that some results were of any clinical relevance or statistical significance [135, 136].

Publication bias is a further type of bias to affect clinical trials and meta-analyses [137-139]. This arises when studies are published or not depending on their results and has been well demonstrated in the medical literature [140, 141]. Empirical research consistently suggests that published work is more likely to be positive or statistically significant than unpublished research [142]. Study publication bias will lead to an overestimation of treatment effects and has been recognised as a threat to the validity of meta-analyses [139]. Furthermore, research without statistically significant results takes longer to achieve publication than research with significant results, giving rise to "time-lag bias" [143].

To circumvent these problems with outcome selection and reporting, trialists, trials methodologists and systematic reviewers have, for some time, supported the development of outcome reporting standards for clinical trials, specific to clinical conditions or areas of healthcare. Such standardisation would facilitate the comparison and synthesis of individual trial data and improve the efficiency of research.

1.3.4.2 Outcomes standardisation and Core Outcome Sets

World Health Organisation (WHO)

The concept of outcomes standardisation in clinical trials was first proposed by the World Health Organisation (WHO) in 1981 [144] . A series of consensus meetings between 1977 and 1979 established that, as a minimum standard, clinical trials in oncology should measure the response of the tumour and metastases, duration of response to treatment and acute and long-term adverse effects of therapy.

Outcome measures in rheumatology (OMERACT)

Out with the field of cancer clinical trials, the OMERACT (Outcome Measures in Rheumatology) collaboration has made the most notable advances in outcomes standardisation. OMERACT is an independent initiative of international health professionals interested in outcome measures in rheumatology, and whose aim is to improve outcome measurement in rheumatology through the development and implementation of Core Outcome Sets (COS) through 'data driven' consensus processes involving relevant stakeholder groups [145]. Although initially limited to improving outcome measurement in clinical trials in rheumatoid arthritis, OMERACT's remit has expanded across the spectrum of rheumatology intervention studies and they have developed a conceptual framework for developing COS in rheumatology [146].

IMMPACT (The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)

IMMPACT aims to develop consensus reviews and recommendations for improving the design, execution and interpretation of clinical trials of treatments for pain in adults and children [147].

HOME (Harmonising Outcome Measurement for Eczema) Initiative

The HOME (Harmonising Outcome Measurement for Eczema) Initiative is an international group working to develop COS to include in all eczema trials [148].

The COMET (Core Outcome Measures in Effectiveness Trials) Initiative

The COMET Initiative (www.comet-initiative.org) was founded in 2010 with the aim of facilitating the development and application of Core Outcome Sets (COS) in all areas of healthcare. It defines a COS as 'an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care' [117]. The consistent use of COS in clinical trials has the potential to increase the evidence base for a particular condition or intervention by allowing results to be compared and combined as appropriate; contributing more data for meta-analyses. COS have the added benefit of ensuring that data from even small studies are not wasted. This is particularly important for less common conditions such as OPSCC, where study populations are already being refined on the basis of biologic tumour features.

COMET's specific objectives are to [149]:

1. Raise awareness of current problems with outcomes in clinical trials
2. Encourage COS development and uptake
3. Promote Patient and Public Involvement (PPI) in COS development
4. Provide resources to facilitate these aims
5. Avoid unnecessary duplication of effort
6. Encourage-evidence based COS development

The COMET initiative website houses a database which is a repository of studies relevant to the development of COS. Website and database usage have increased significantly over time reflecting the growing interest in this field [150, 151]. The Cochrane collaboration and the National Institute for Health Research, the largest

funder of healthcare research in the UK, advocate the use of COS, and, in their grant applications, the NIHR Health Technology Assessment funding body asks that COS be used if they exist in the area of healthcare to which the trial applies [152]. Furthermore regulatory bodies [153, 154] and journal editors [155] are now calling for the use of and/or development of COS.

1.3.4.3 Patient inclusion in choosing the outcomes measured in trials

Until relatively recently, patients were seldom involved in trial design or in making recommendations for the outcomes of importance. One of the first groups to integrate patients into this process was OMERACT. Patient involvement in outcome selection was initially proposed at the OMERACT meeting in 2000, when clinicians struggled to answer the question of what would be defined as a 'clinically important change' in response to treatment. Patient involvement in subsequent OMERACT meetings helped to enrich the research agenda by identifying novel outcomes and instruments of relevance [156]. New outcomes, of significant value to patients, were identified and integrated into the core set for rheumatoid arthritis (RA) clinical trials.

A number of groups in the UK now value patients as major stakeholders in setting the research agenda and in contributing to decisions about which outcomes should be measured in clinical trials. The James Lind Alliance (http://www.jla.nihr.ac.uk) brings patients, carers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritise the Top 10 uncertainties or unanswered questions about the effects of treatments. Their aim is to make sure that health research funders are aware of the issues that matter most to patients and clinicians. INVOLVE (http://www.invo.org.uk) is a national advisory group whose role is to bring together expertise, insight and experience in the field of patient and public involvement (PPI) in research, with the aim of advancing PPI as an essential part of the process by which research is identified, prioritised, designed, conducted and

disseminated. The Core Outcome Measures in Effectiveness Trials (COMET) initiative have launched the People and Patient Participation, Involvement and Engagement (PoPPIE) working group to lead and oversee the public participation, involvement and engagement work of the COMET initiative in promoting and facilitating Core Outcome Set (COS) development and uptake [157].

1.3.4.4 Improving the transparency of clinical trial reporting

The Consolidated Standards of Reporting Trials (CONSORT) statement is a set of recommendations for the reporting of randomized trials in healthcare [158]. Published in the 1990s, it sets out the essential items that should be included in reports of RCTs, aimed at primary reports of RCTs with two group, parallel designs. The content of CONSORT focuses on items related to the internal and external validity of a trial. The main aim of CONSORT is to provide guidance to authors about how to improve the reporting of their trials, and whilst not originally intended as a quality assessment instrument it may allow readers, peer reviewers and editors to critically appraise and interpret reports of RCTs [159]. The CONSORT guidelines have been updated twice since their inception [159, 160] and there are many trial design specific extensions and specifically one for the reporting of patient reported outcomes [116]. A 2012 Cochrane review to assess the impact of the use of the CONSORT statement on completeness of reporting of RCTs published in medical journals suggested that journal endorsement of CONSORT may benefit the completeness of reporting of RCTs they publish. However, despite relative improvements when CONSORT is endorsed by journals, the completeness of reporting of trials remains sub-optimal. Fidelity of endorsement by journals has been weak to date [161].

1.4 Rationale for the work in this thesis

There is strong evidence that heterogeneity of outcome reporting in effectiveness trials hampers the synthesis of trial data in meta-analyses in oncology [162-165]. Variability in how outcomes are defined or measured can make it difficult or impossible to synthesise and apply the results of different research studies [166]. The outcomes selected are often not those that are regarded as important by patients [167] and different reporting methods and study outcomes create high data redundancy and costs [168]. These methodological problems lead to delays in establishing the relative effectiveness of interventions and, a frequent conclusion of systematic reviews and meta-analyses in SCCHN and OPSCC is a call for greater consistency in the outcomes measured in comparable trials [100, 169-171].

A series of Cochrane reviews of interventions for the treatment of oral cavity and oropharyngeal cancer published between 2010 and 2011 found a number of problems with outcome reporting. The review of radiotherapy interventions found that adverse events were poorly reported and the authors concluded that 'more accurate methods of reporting adverse events are needed in order to truly assess the clinical performance of different radiotherapy regimens' [170]. The review of chemotherapy interventions originally sought to evaluate the benefits of chemotherapy in addition to loco-regional treatments, against the potential increase in the adverse effects of treatment associated with toxicity [169]. However, toxicities and adverse events were often reported as numbers of events rather than numbers of patients with adverse events, and there was considerable variation in the way harms were reported. As such, there was so little quantitative data in the reports regarding harms associated with treatment, the protocol had to be modified to report only the benefits associated with chemotherapy, in terms of survival and response to treatment. This is an important omission, given the known increased toxicity associated with the addition of chemotherapy [172]. Furthermore, the authors commented that 'The large quantity of research on chemotherapy focused

on finding better treatments that prolong overall survival, disease free survival and progression free survival. Quality of life is inconsistently reported in trials which address a primary outcome of overall survival'. The review of surgical interventions by Bessell et al. [171] found the overall quality of the evidence to be poor, with all included studies having either a high or unclear risk of bias. This is less surprising in the context of trials in surgery where it is both difficult and possibly unethical to blind trial participants. There was little data in the included studies regarding the patients' HRQOL which made it difficult to fully assess the benefits and harms of the different surgical procedures. A 2016 Cochrane review by Howard et al. of minimally invasive surgery (Trans-oral laser microsurgery or Trans-oral robotic surgery) versus radiotherapy/chemoradiotherapy for small-volume primary OPSCC found that no completed studies met the inclusion criteria for the review. There is currently no high-quality evidence from RCTs regarding clinical outcomes for patients with OPSCC receiving minimally invasive surgery compared with primary chemoradiotherapy [173]. The MACH meta-analysis, perhaps the most seminal meta-analysis in SCCHN, which looked at the benefits of adding chemotherapy to loco-regional treatment found that clinical heterogeneity and trial design were significant barriers to establishing conclusions regarding effectiveness [100].

The aim of this research was to develop a COS for clinical trials in OPSCC. At the induction of this research, I intended to develop a COS for clinical trials in all SCCHN subsites. However, it soon became clear that reaching consensus on 10 or fewer outcomes of key importance would be difficult, and probably futile because of the heterogeneous nature of the disease. As already discussed, tumours arising from different anatomical sub-sites - and even between individuals with tumours at the same sub-site, exhibit substantial differences in tumour behaviour, response to treatment and choice of treatment strategy. These differences provide challenges when choosing which outcome to measure in clinical trials in SCCHN; the

outcomes important to someone with laryngeal cancer may not be the same as or even relevant to someone with an oral cancer.

The rising incidence of OPSCC, in a younger population and the associated rise in de-escalation trials in this area prompted us to focus our efforts on developing a core outcome set for OPSCC. Furthermore, the changing patient demographic caused us to question whether the short- and long-term outcomes associated with contemporary treatment strategies were deemed acceptable to patients, who will live for longer with adverse effects of treatment and therefore may have higher functional and HR-QOL expectations. We wished to understand which outcomes were important to patients when survival became less of an uncertainty.

The importance of this decision was underlined by discussions with our Head and Neck cancer multi-disciplinary team, and, in particular, speech and language therapists. There was an acute recognition that future treatment strategies would need to ensure better functional outcomes for long-lived survivors.

A 2016 systematic review by Blanchard et al. which aimed to establish outcomes priorities for patients with SCCHN found that studies relating to OPSCC were heterogeneous in both design and endpoints, complicating the ability to draw meaningful conclusions about which outcomes of treatment OPSCC patients prioritise [174]. This study emphasized the need for future research to harmonize outcome measurement.

The focus of the work undertaken in this thesis is to address issues of outcomes heterogeneity and poor quality outcome reporting by developing a COS for clinical trials in OPSCC. I will do this using methodology advocated by the COMET initiative, and in particular, the following questions will be explored:

- Is outcomes heterogeneity a problem in contemporary RCTs in OPSCC

- Which outcomes are measured in contemporary RCTs in OPSCC
- Which outcomes are important to patients and healthcare professionals
- Is there consensus regarding the outcomes of importance

This research study was entitled The CONSENSUS (Squamous Cell CarcinOma of the OropharyNx: Late PhaSE CliNical TrialS; Core OUtcomeS) study, and this name was used in all study literature and presentations and publications arising from the research.

1.4.1 Aims and objectives

1.4.1.1 Aims

1. To develop a COS for use in OPSCC clinical effectiveness trials including both patients' and healthcare professionals' perspectives
2. To investigate patient experiences of OPSCC

1.4.1.2 Objectives

a. Develop a comprehensive list of outcomes of OPSCC informed by the literature and qualitative interviews with patients
b. Use the list to develop a questionnaire to survey patients and healthcare professionals on the importance of each outcome
c. To use qualitative interviews to understand the patients' experiences of living with OPSCC
d. Identify the outcomes most important to patients and healthcare professionals (COS) using Delphi consensus methods

1.4.2 Methodological approaches in COS development

At the outset of this research, no formal guidance existed for those wishing to develop COS. A number of different methodological approaches had been taken by different COS developers. Although, now superseded by the COMET handbook, published in 2017 [117], in 2012 Williams et al. made recommendations for the important issues to consider when developing a COS which informed the work in this thesis [152]. This included:

1. Identifying existing knowledge
2. Establishing the scope of the COS
3. Stakeholder involvement
4. Use of consensus methods

In the COMET handbook [117], this has been expanded upon, and a four-stage COS development process is now recommended:

Step 1. Define the scope of the COS

Step 2. Check whether a new COS is needed

Register the COS in the COMET database

Step 3. Develop a protocol for the development of the COS – the 'what' to measure

Step 4. Determine 'what to measure'

(i) Identify existing knowledge

(ii) Fill gaps in knowledge if needed

(iii) Elicit views about important outcomes in a consensus process

(iv) Hold a face to face meeting to finalise the recommended COS

(v) Report the work using the COS-STAR guidance

A further step, beyond the scope of identifying 'what to measure' advises on steps to take to determine 'how to measure' (Step 5) the COS. Throughout the COS development process and once it is published, implementation must be considered and uptake assessed. The COS must be reviewed and updated as necessary.

As our COS was developed prior to publication we made the following considerations in line with the available recommendations at the time:

Identifying existing knowledge

One of the objectives of COMET is to avoid duplication of COS research, and by holding a regularly updated database of COS studies, they can advise potential COS developers on whether a COS already exists or is in development in a particular clinical area. This is also directly searchable via the COMET database [175]. A review of previous trials or a systematic review in the area can provide evidence of the need for a COS and also identify a list of potential outcomes [176]. We consulted the COMET database and the COMET study team at the outset of this research to establish whether there were any existing COS for clinical trials in SCCHN or OPSCC or any registered projects aimed at developing COS for SCCHN or OPSCC. We also performed scoping searches of the literature in case any important work had been missed by the COMET database developers.

Establishing the scope of the COS

Most COS apply to a clinical condition, however, they may be more specific than this and apply to, for example, glue ear in children with cleft palate [177]. Similarly they may apply to all interventions or only specific ones, for example to surgery for colorectal cancer, but not other interventions [178]. It is important to establish from the outset to which patients, interventions and clinical condition(s) the COS will apply as this will almost certainly affect how the research to identify the key outcomes for the COS is conducted.

Our COS was limited to late phase clinical trials of interventions available at the time of designing the COS, namely surgery, radiotherapy, chemotherapy and immunotherapy. The COS was designed for trials with curative intent in HPV-positive and HPV-negative patients. We felt that the outcomes of most importance for trials of interventions in patients with recurrent or metastatic disease were likely to be different to those in primary disease, with interventions of curative intent.

COS are not necessarily comprehensive. The outcomes identified should represent the *minimum* that should be measured and reported. Additional outcomes are encouraged and should be chosen at the discretion of the trials team bearing in mind the circumstances of the study. A COS containing many outcomes may be a barrier to implementation in clinical trials as this will increase outcome measurement, and in all likelihood, the resources required and the cost of the trial.

The first stage in COS development is to identify the outcomes that should be measured, once this is established, research to identify how these outcomes should be measured can be undertaken. The COMET initiative facilitates collaborations between COS developers and COSMIN (Consensus-based Standards for the selection of health Measurement Instruments.) who make recommendations about '*how'* the identified outcomes should be measured [179]. COSMIN aims to improve the selection of outcome measurement instruments (OMIs), and has developed methodological standards for studies on the measurement properties of OMIs [180].

Stakeholder involvement

Key stakeholders should be identified and invited to participate in deciding which outcomes should be included in the COS. They may be participants in identifying possible outcomes and/or in consensus exercises to prioritise the contents of the

COS. Key stakeholders will almost always include patients and healthcare professionals with knowledge of the clinical condition, but this could also include regulators, industry representatives and researchers.

COMET differentiates between patient and public participation in research and patient and public involvement (PPI). Research participants take part in research which is "to", "about" or "for" them. In contrast, PPI refers to research where patients are involved in designing the study; where research is 'being carried out "with" or "by" members of the public [181]

Patients, carers and healthcare professionals were all involved in this study, both as research participants and in facilitating certain methodological decisions, and providing guidance on certain aspects of study conduct. In seeking to identify a list of possible outcomes to be included in the COS we undertook a series of qualitative interviews with OPSCC patients and carers and in ratifying the contents of the COS through consensus methods we involved OPSCC patients, carers and a number of different types of healthcare professional. COMET's PPI co-ordinator, Heather Bagley, advised on patient and carer information sheets and on some of the qualitative aspects of the study. I chose not to interview healthcare professionals as I felt the systematic review would adequately identify outcomes of importance to healthcare professionals. In most cases, it is unlikely that a diversity of healthcare professionals will be involved in outcome selection in clinical trials, as discussed in the relevant chapter, the use of consensus methods amongst a diversity of healthcare professionals allowed us to identify differences in the outcomes prioritised by the different stakeholder groups.

Use of consensus methods

For any condition, there are likely to be multiple outcomes that could be included in a COS, and stakeholders may differ in their opinions about which outcomes to include. For these reasons, group consensus methods are frequently employed to

both elicit opinion on outcomes of importance and refine a long list of possible outcomes to an agreed list of around ten or less for the COS. Expert panel meetings, sometimes using nominal group techniques, and Delphi studies are the methods used in previous COS studies to elicit opinions and develop consensus [152]. The ability of the method to achieve true consensus amongst a diverse range of stakeholders with methodological rigour is the most important consideration. However, one must also bear in mind factors such as practicality and cost.

The nominal group technique employs a highly-structured face-to-face meeting of relevant stakeholders to both elicit opinion and reach consensus on a given topic. Meetings usually comprise 5-9 stakeholders and last around 2 hours [182]. Stakeholders are coordinated by a facilitator to ensure participation by all. Although the specifics will vary for different purposes, that used in healthcare seems to follow a similar pattern to that described by Potter et al [182]. In the first stage of the process participants are introduced and an explanation is given of the purpose of the session. Information sheets may be given and consent taken along with the setting of 'ground rules' around confidentiality, respect and protection of participants' identity [183]. This is followed by the 'silent generation of ideas' in response to a number of questions. Participants are then invited to share their ideas using a 'round robin' technique until all ideas have been presented. Discussion is discouraged until all ideas have been recorded so that each participant has the opportunity to share their opinion prior to it being modified or rejected by the group. Once all responses are listed, group discussion can ensue to clarify ideas. Finally, participants are asked to prioritise their ideas about each question discussed. The number of meetings required will depend on the nature of the question and accessibility of stakeholders, for healthcare issues, a number of meetings are normally required and should only conclude, like focus groups, when now new ideas are being generated i.e. data saturation is achieved [182, 184, 185].

The Delphi technique was originally developed by the RAND corporation in the 1950s in order to forecast the influence of technology on warfare [186]. Whilst the specifics of conduct vary between studies, this method comprises sequential questionnaires answered anonymously by a panel of participants with relevant expertise. After each questionnaire, the group response is fed back to participants who are asked to reflect on and possibly change their voting in light of how other participants have voted to move towards group consensus. There must be at least two rounds in a Delphi study to allow reflection on the previous rounds scores. There may also be a 'blank paper' round to elicit opinion prior to scoring items.

Over NGT, one of the advantages of the Delphi method is that it is anonymous. Participants do not meet face to face and there is less chance of more vocal or authoritative figures dominating the discussion or influencing others' voting. Additionally, participation can be done remotely using postal or online surveys, and therefore location is of no barrier to participation, which means a more diverse and numerous group of individuals can participate. For these reasons it has become the most popular choice of consensus method for developing COS [117].

Study protocol

There are potential sources of bias in the COS development process, and in their handbook, COMET recommend that a protocol be developed prior to the start of the study, and made publicly available. In order to improve transparency and share methods with others we published the protocol for this study in an open access journal [187]. There was significant interest in the protocol which was 'highly accessed' in the first few months of publication.

Project registration

The COMET initiative aims to provide a means of identifying existing, ongoing and planned COS studies. The COMET database acts as a repository for such studies and is a free-to-access, unrestricted public repository which maximises the

potential of potential COS developers finding relevant studies, thereby avoiding duplication of effort and facilitating collaboration. The project was registered with the COMET database in 2011.

1.4.3 Methods employed in this research

The COMET handbook describes what is currently known about COS development, implementation, review and uptake, yet, there is no gold standard method for developing COS and research to identify optimal methods is ongoing [188]. In the handbook, for some areas of COS development there are 'recommendations for practice, in other areas 'issues to consider', and areas highlighted where there is a need for further research.

Most COS developers employ a mixed methods approach in order to ensure adequate identification of outcomes, stakeholder involvement and consensus opinion. A mixed methods approach is commonly used by COS developers to identify outcomes for inclusion (systematic review, interviews, surveys), and then establish which of the possible outcomes should be included in the COS, using stakeholder consensus techniques. Mixed methods approaches combine elements of qualitative and quantitative research with the broad purpose of increasing the breadth and depth of understanding [189]. Such 'methodological triangulation' was helpful in this work as it allowed me to investigate and understand the perspectives of different stakeholder groups and engage them in a consensus exercise to identify outcomes of key importance. This comprised the steps shown in figure one and discussed below and in the forthcoming chapters two, three and four.

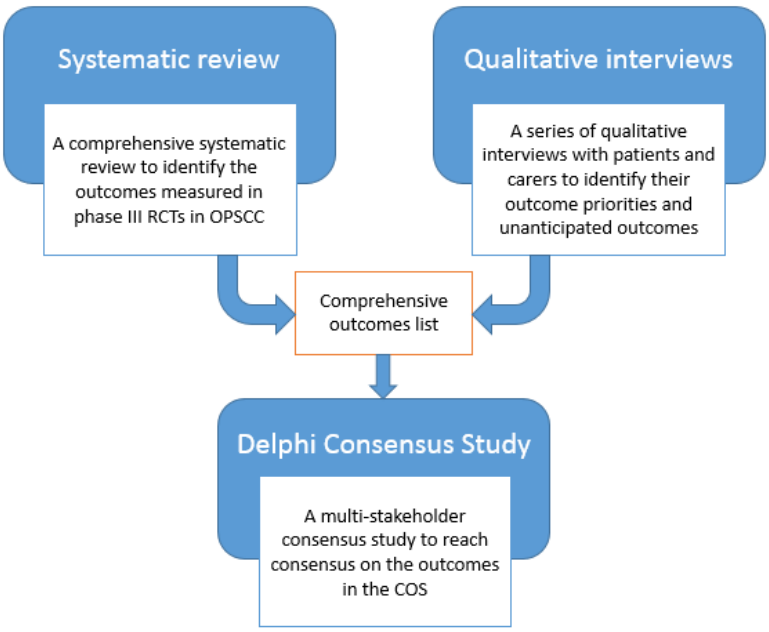


Figure 1 Mixed methods approach

1.4.3.1 Identifying existing knowledge

I started out by identifying existing knowledge and COS research in SCCHN and OPSCC. No COS studies were registered with the COMET database, however scoping searches identified a conference abstract for a study to develop an 'outcomes toolbox' for use in SCCHN clinical trials. The purpose of this study was not to establish which outcomes were important, rather, to identify a set of instruments suitable for widespread application in the conduct of clinical trials for SCCHN, allowing non-specialists to accurately evaluate the acute and late toxicity of a regimen and its impact upon a patient's quality of life (QOL) and function. This instruments were chosen by a group of healthcare professionals and patients were not involved at any point in the design or conduct of the study. I made three attempts at the time to contact the lead author of the abstract, as there could be some cross-over in the research, however I received no response. The 'outcomes toolbox' has subsequently been published [190].

The previously mentioned ICF core sets for SCCHN were also identified in these scoping searches [122, 191-193]. Although the ICF is widely comprehensive it does not include outcomes such as death, an outcome that is especially important to measure in clinical trials investigating treatments for life threatening illnesses such as cancer.

1.4.3.2 Systematic review

The previously mentioned series of Cochrane reviews of interventions for the treatment of OPSCC had identified heterogeneity in the reporting of outcomes between OPSCC clinical trials [169-171]. I therefore felt it was pertinent to examine the outcomes measured in OPSCC RCTs through a systematic review of the literature. I wished to establish whether there was any standardisation in the outcomes measured, which outcomes were measured and thus which outcomes were important to trialists and clinicians, as they select the outcomes in trials. The outcomes identified would be added to a comprehensive outcomes list to be used in the development of a Delphi Consensus Study.

Systematic reviews are an efficient way of identifying outcomes used by researchers in a particular clinical area, they do however just aggregate the opinions of the previous researchers on what outcomes they deemed important to measure. We therefore knew that we would have to involve researchers in the later phases of the study to ensure consensus development in the wider community of stakeholders.

We decided not to include qualitative studies or other study types in our systematic review, only RCTs. This was decided a priori, for the following reasons:

1. We had established from previous research that PROs were poorly reported in the literature

2. We intended to interview OPSCC patients and carers, to establish the experiences of those going through treatment, particularly in relation to PROs
3. As chemoradiotherapy was the current standard of care for patients with OPSCC at the outset of this research, we knew that there were a significant number of RCTs from which to draw outcomes
4. Including all study types would have significantly increased the amount of literature to search and resources were not available for this within the constraints of this project
5. We wished to establish the outcomes used in effectiveness trials as this is the type of trial to which the COS would apply

There is no recommended time window to conduct systematic reviews, however we wished to include contemporary RCTs and so restricted our search to the preceding ten years. Another strategy is to start with a smaller time window and test for outcomes saturation by extending the search and comparing the results. If no new outcomes are identified, the search can be limited in timeframe. Our data extraction was consistent with that now recommended in the COMET handbook, considered in terms of:

1. Study characteristics
2. Outcomes
3. Outcome measurement instruments and/or definitions provided by the authors for each outcome

Also, as is now recommended in the handbook, we extracted the outcomes verbatim, the synthesis of the same outcomes with different verbatim terms is also clearly described. In contrast to recommendations in the handbook, I did not perform a specific PROM review or extract PROs from PROMs, I also did not search for qualitative studies for outcomes.

1.4.3.3 Qualitative interviews

To identify the outcomes of most importance I felt it would be appropriate to ask those with experiential knowledge of OPSCC and treatments for OPSCC; patients and those who care for them. We know that adverse effects of treatment for head and neck cancer are common; they are frequently quantified, but few researchers have tried to establish the significance of these adverse effects to patients in trying to choose between treatments. By understanding this, and where these outcomes sit alongside outcomes relating to disease control and survival, we can better understand patients' and carers' outcome priorities. The COMET initiative advocate seeking patient opinion about the outcomes to be included in a core outcome set. We felt this to be of the utmost importance in this instance as we suspected that functional outcomes would be of significant concern to patients. The changing patient demographic demands that we question whether the outcomes identified as priorities for OPSCC patients in previous research, still apply. We also wished to ensure that important outcomes were not overlooked from the comprehensive outcomes list identified from the systematic review and to understand the ways in which patients describe outcomes, to inform the Delphi consensus study, and possibly inform *how* outcomes should be measured.

Other COS developers have used qualitative methods in COS development to access perspectives of groups such as patients, carers, members of the public and healthcare professionals because these views may not be encompassed in a systematic review of outcomes [177, 187, 194, 195]. Furthermore, participation in COS development may be more meaningful to certain groups when qualitative methods are employed.

Qualitative methods may be used:

1. To identify the outcomes of relevance to the whole stakeholder community

2. To preserve the distinct perspective of different stakeholders
3. To help make consensus processes accessible to patients
4. To inform deliberations in the final stages of COS development
5. To address gaps in existing COS

In certain circumstances, the use of qualitative methods may be particularly helpful. If all potentially important outcomes have not been identified before a consensus process, qualitative interviews could help ensure that no potentially important outcomes are missing. Retention of Delphi participants can be problematic and qualitative studies may help to minimise the number of rounds (by allowing for omission of the open 'blank' round). Qualitative methods may help to define the scope of the COS, population and interventions to be covered and provide insight into why certain outcomes are important to patients.

Discussions with the Mersey Head and Neck Cancer Patient and Carer Research Forum informed our decision to use qualitative interviews over other forms of qualitative inquiry. We had considered conducting a focus group to elicit opinion on outcomes of importance, however the forum felt that the issues were highly emotive and that discussing these with others present would be difficult for patients and carers. They felt that patients would hold back and that carers may not want to speak openly about their perceptions of the patients' experience; it might seem that they were somehow undermining the patients' experience as they didn't go through treatment themselves. They agreed, however, that carers could provide a unique insight into the condition and treatment, and suggested a focus group after the interviews if there was concern that important outcomes were missing.

We chose not to interview healthcare professionals because we were considering their opinion when eliciting outcomes through the systematic review and later in the Delphi survey. Clinical and non-clinical trialists choose the outcomes to be measured in clinical trials, and we felt the review would therefore encompass their

opinion on outcomes of importance. Furthermore, the first round of the Delphi survey had a 'blank sheet' to elicit further opinion on outcomes of importance. Healthcare professionals from multiple stakeholder groups were invited to participate in the Delphi survey to increase the diversity and experience of those participating.

1.4.3.4 Delphi Study

A Delphi Study was used to elicit views of participants on outcomes of importance and reach a consensus about which outcomes should be included in the COS. In the case of our research, the advantage of this approach was that it is not face-to-face, and avoids the problem of more vocal or apparently senior participants dominating the group discussion and therefore influencing others' voting, as was the risk with a patient/clinician cohort. Secondly, we wished to achieve international consensus and online Delphi methods allowed us to do this without incurring any additional costs.

As previously stated, the COMET handbook was not published at the time of conducting this research, however it discusses the important methodological considerations when designing a Delphi survey in some detail. I contributed to a qualitative study of COS developers undertaken by the COMET initiative as an interviewee and discussed several of these methodological considerations, as I encountered them during the course of this project [196]. These include [117]:

The number of panels

This depends on the stakeholders required and the way in which it is felt appropriate to their opinions. The single homogenous panel approach will result in core outcomes deemed essential by a one stakeholder group e.g. patients with the clinical condition under study or knowledge of this. In a single heterogeneous panel, the views of multiple stakeholder groups are combined. Feedback and

criteria for consensus are based on the group overall and careful consideration and justification is needed of the panel mix, because the resulting core outcomes may depend on the relative proportions of stakeholders participating i.e. be weighted towards the views of a particular stakeholder group. Where differing stakeholder opinions are anticipated, multiple homogenous panels in which feedback and criteria for consensus are isolated to a single stakeholder group have distinct advantages. The final COS or outcomes taken forward to the next stage of COS development are likely to consist of the outcomes deemed essential by all stakeholder groups

Group size

There are no statistical methods for calculating power or sample sizes for Delphi studies. This is often a pragmatic choice and will depend to some degree on resources and the clinical condition and number of experts available. It is most important to ensure representation from key stakeholder groups with individuals with a deep understanding of the issues. However the greater the number of participants, the more likely the COS is to be generalisable to future patients and in convincing others of its value.

Participant information

Well informed participants will contribute more meaningfully to the consensus process and it is essential that participant information is tailored to the individual groups to enable informed consent and equip participants to be able to score and prioritise outcomes.

Number of rounds

There must be at least two rounds in a Delphi survey, including at least one round of feedback. The number of rounds will depend to some degree on the amount of work already performed in eliciting stakeholder opinion. Some studies have used open-ended rounds with no voting to elicit opinion as an alternative to performing

a review of the literature. The number of rounds does not have to be pre-determined but criteria for selecting an end-point should be defined. Although consensus will not be reached on all outcomes it is necessary that a reduced number of outcomes has been agreed, in line with a pre-defined stop criterion.

Structure of questionnaires

It is important that questionnaires are tailored to the individual stakeholder groups, avoiding jargon that would be unfamiliar. Anecdotal evidence from the piloting of Delphi questionnaires for COS for cancer surgery and otitis media with effusion in children with cleft palate suggest that lay terms are preferred to medical terms, even by healthcare professionals. Stakeholder involvement in the design and piloting of the Delphi questionnaire is recommended.

Order of questionnaire items

There is evidence from one nested methodological study within a COS study that the order in which outcomes are delivered affects their scores and ultimately consensus [197]. Chalmers et al. presented clinical and patient reporting outcomes (PRO) in varying orders to participants developing a COS for oesophageal cancer. They found that patients were more likely to rate PRO items as essential when they appeared last in the questionnaire, whereas professionals were more likely to rate them as essential when they appear first.

Additional open questions

There are different methods for identifying an initial long list of outcomes to inform the Delphi survey. This list can be added to by eliciting opinion with an open question round or section of the first round of the Delphi. Whatever the method, criteria for adding additional items should be stated i.e. any new outcomes or only those suggested by two or more respondents might be added.

Scoring system

Most COS studies have used a Likert type scale with outcomes scoring 1-3 deemed not important, 6-8 important but not essential and 7-9 essential [177, 198, 199]. This system is a framework recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for assessing the level of importance about research evidence [152, 199]. Other studies using a Likert type scale have simply stated 1 as 'not essential' and 9 as 'absolutely essential' and asked participants to vote somewhere on this scale [200, 201]. Other studies have asked participants to divide a total number of, say 100 points between all of the outcomes [202] and others still to rank all outcomes [203].

Feedback between rounds

Reaching consensus requires reconciliation of different views. In a Delphi this is achieved by providing feedback after each round on how other participants have voted in that round. This allows reflection on how others have scored before re-rating in the following round. At the end of each round the results for each outcome are aggregated and descriptive statistics presented. The way in which results are aggregated and presented depends on the number of panels and if the scoring is weighted by stakeholder group. There are currently no best practice guidelines on the best way to summarise and present feedback and there is methodological research within ongoing COS studies to evaluate this.

Retaining or dropping items between rounds

After the initial Delphi round, outcomes not reaching the pre-defined cut off may be dropped (not presented in the subsequent round) or kept and re-presented in the second round. If items are dropped after the first round, participants will not get the opportunity to re-score those outcomes taking into account feedback on scores from other participants. If however, the initial list of outcomes is large, including all outcomes in each Delphi round may impose sufficient burden on participants to increase attrition from one round to another [117].

Attrition and attrition bias

Attrition rates vary between studies and seem to depend to some degree on the method of recruitment; attrition rates are reported to be higher in studies using a less targeted recruitment approach, somewhere in the region of 15 - 20% between rounds [198, 204]. There is no guidance on what constitutes an adequate response rate, however around 80% for each stakeholder group is deemed satisfactory in most situations [117]. There is little evidence regarding the impact of attrition bias in COS studies, however it is likely to be more methodologically sound to compare average scores for each outcome between groups than average scores for all outcomes.

Defining consensus

A number of different criteria have been used to define consensus. One of the most commonly employed approaches in recent COS studies is a version of that used by Wylde et al. (2015). They implemented a threshold for inclusion in the core set of 70% of participants scoring outcomes as 7 to 9 and 15% or less scoring 1 to 3 to be met by both the clinician and patient panels or 90% or more scoring 7 to 9 from any single panel [205]. Harman (2015) [177], Potter (2015) [200] and Blazeby (2015) [201] have all used a '70/15%' cut-off.

Assessing the degree of consensus

An assessment of the degree of consensus between rounds is advisable to ensure that the Delphi is working as a consensus technique.

1.5 Structure of the thesis

Following on from this unified introduction, the individual components of this study will be presented in three different chapters. Chapter two will present the methods and results of a systematic review to identify the outcomes currently

reported in OPSCC RCTs; chapter three will present the methods and results of a series of qualitative interviews with patients and carers to establish the outcomes they believe are important and chapter four the Delphi study methods and results. In chapter five, I will discuss the recommendations for the contents of a COS for OPSCC clinical trials and consider the limitations of the study; in chapter six I will identify areas for future work.

Chapter 2

A systematic review to identify the outcomes reported in randomized controlled trials in oropharyngeal cancer

2.1 Rationale for this chapter

This systematic review was conducted to identify the outcomes reported in contemporary RCTs of interventions for the curative treatment of OPSCC. As outcomes in RCTs are chosen by clinical and non-clinical trialists, this is likely to identify the outcomes these stakeholders prioritise and deem most worthy to measure in OPSCC RCTs.

The comprehensive list of outcomes identified in this review was categorised by the study team; comprising two otolaryngologists, a trials methodologist and a qualitative researcher; and carried through to a consensus process to ratify the outcomes to be included in the final core outcome set.

2.2 Objectives

To identify, summarise, compare and critique the outcomes reported in RCTs of interventions for the treatment of OPSCC.

2.3 Methods

This systematic review adhered to a predefined protocol, published in 'Trials' http://www.trialsjournal.com/content/15/1/168, see Appendix one [74].

2.3.1 Inclusion criteria

Phase III RCTs of interventions for the curative treatment of OPSCC, including SCCHN RCTs that comprise patients with OPSCC, and RCTs including only patients with OPSCC. Trial participants were adults over the age of 18, with a first diagnosis of OPSCC who hadn't had any other form of treatment. The review was limited to human studies in the English language published between 1 January 2003 and 14 May 2013 to restrict the review to evaluations of current practice. Open-label trials were included.

2.3.2 Exclusion criteria

RCTs including patients with recurrent or metastatic disease and those of interventions for the sequelae of treatment, such as xerostomia were excluded. Abstracts and conference reports without corresponding published articles were excluded because the information was likely to be incomplete.

2.3.3 Identification of studies

We identified studies by searching electronic medical literature databases and by hand searching relevant systematic reviews. Scoping searches had been conducted at the outset of the study first to identify any existing COS work in OPSCC, and secondly to identify important RCTs.

2.3.3.1 Search strategy and information sources

To optimise our chances of identifying all relevant studies, we searched a variety of medical literature databases. The Cochrane Central Register of Controlled Trials (CENTRAL) is the most comprehensive database of RCTs [206], this database contains citations to reports of clinical trials from a wide range of sources. The

Cochrane Handbook recommends that supplementary searches of both MEDLINE and Embase are undertaken too [206]. There is a time lag of approximately one to two years with respect to Embase records appearing in CENTRAL. Over Medline, PubMed has the advantage that it includes in process records. The lead author (AW) therefore performed electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Embase.

The search strategy was adapted iteratively from one developed for a review by the Cochrane Ear, Nose and Throat disorders group to identify all RCTs in OPSCC. On initial testing, the search strategy failed to pick up several key papers, identified in early scoping searches, we therefore had to truncate this, ending up with a broad search strategy and therefore a large number of identified studies. Attempts to rationalise the search strategy still led to the exclusion of eligible studies and we therefore had to accept a search strategy with a high sensitivity, but low specificity.

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials was implemented and combined, using the Boolean operator "AND" with MeSH terms for OPSCC and SCCHN. Systematic reviews were excluded by combining this with the Boolean operator "NOT" for ("systematic review" OR "meta analysis") OR "Cochrane Database Syst Rev". Truncations were used to improve the sensitivity of the search. The strategy was developed for PubMed (Appendix two) then translated for CENTRAL and Embase, to allow for differing subject index terms and RCT filters. Endnote reference management software was used to import the identified records. Cochrane reviews of interventions for the treatment of oropharyngeal cancer [169-171] were hand-searched and cross-referenced with the search findings; this process was conducted by 2 reviewers (AW and KL).

2.3.3.2 Study selection

Two reviewers (AW and LW) independently assessed the identified records. A three phase exclusion process was implemented.

Phase I – exclusion by study title

All identified records were reviewed by title, and studies that were ineligible were excluded. A single reviewer (AW) made an initial assessment of all study titles, and subsequently re-reviewed a random sample of 100 excluded studies and their abstracts to ensure accurate exclusion. A second reviewer (LW) assessed full papers for 40 of the excluded studies at title, to check for accuracy of exclusion.

Phase II – exclusion by abstract

Studies that were eligible from the title or for which there was uncertainty, had their abstracts reviewed in the second phase.

Phase III – exclusion at full paper review

AW reviewed all studies and LW assessed a proportion of these. In order to ensure accurate exclusion, a proportion of all included/excluded titles, abstracts and full papers were reviewed by the senior authors (TMJ and CTS). Any disagreement between AW and LW was also discussed with the senior authors.

2.3.4 Data extraction

Data was extracted from eligible studies directly into an excel database by one reviewer (AW) and, for a selection of studies, cross checked by a second reviewer (LW). For each study, the following data were extracted:

- Outcomes reported, their definitions, methods of measurement and whether they were a primary or secondary outcome
- Outcome on which sample size was based, whether a sample size calculation was performed and whether sample size was recruited
- General study features: interventions, number of participants, proportion of OPSCC participants
- Participant characteristics comprised age, gender, disease stages and sub-sites

All outcomes reported in the results were extracted whether or not they were specified in the methods as outcomes, and all outcomes stated in the methods were extracted whether or not they were reported in the results. Outcomes were judged to be defined if they were described in the text or referenced with a citation. Acute and late toxicity were said to be defined if they were either described in the text or measured using a validated tool. The individual outcomes within composite toxicity and HR-QOL patient reported outcome measures (PROM) were not extracted or analysed separately as they were so incompletely reported. Furthermore, we wished to undertake qualitative interviews with patients and carers later in the study to establish PROs of importance.

Outcome definitions were compared and outcomes with the same definitions were merged under outcome domains using the verbatim term most commonly used for the outcome described. Outcomes with the same verbatim term but contrasting definitions were not synthesised, and will be described later. The mapping of individual outcomes to domains was undertaken by (AW) and then checked by the whole study team (TMJ, CTS, BY).

As we wished to establish *what* was measured rather *how* it was measured we chose to categorise outcomes into domains, excluding time-points such that three- and five-year loco-regional control were absorbed into ‘loco-regional control’.

Time-points are important, and work to establish the best time-points at which to measure outcomes included in the COS will be conducted after the COS is established.

2.3.5 Assessing the quality of included studies

We recorded intended sample sizes, how these were calculated and whether they were recruited. An assessment was made of the method of randomization, and all adequately randomized Phase III trials that met the eligibility criteria were included, and studies with inadequate randomization were excluded. Blinding method was noted but not part of our eligibility criteria and open-label trials were included.

An assessment of disparities between outcomes stated in the methods and results was initially made, however this was felt to be of little value without actually consulting trial protocols. It would provide inadequate evidence to assess bias, and this was not an objective of the review. Trial protocols were not requested and Cochrane risk of bias assessment [207] or comparison against the CONSORT checklist was not performed [159]. This was decided a priori as the objective of the systematic review was to identify a comprehensive outcomes list for the Delphi, not to make an assessment of bias or methodological rigour in the included studies. The COS-STAR minimum standards for reporting COS studies only specify that the sources of the initial long list of outcomes are identified, not that any other assessment of the sources from which they were extracted is made [208].

2.3.6 Data analysis and presentation of results

Results are tabulated and descriptive statistics used to summarise the data.

2.4 Results

2.4.1 Study selection

The initial database search conducted on 14th May 2013 identified 16,077 records in PubMed, Embase and CENTRAL. Following the removal of 4150 duplicates, 11927 records were screened, and 11845 excluded by title and abstract review. Full-text articles were retrieved and reviewed for 82 studies, of which 51 were eligible. These 51 reports related to 43 published RCTs which were included in the narrative synthesis. (See PRISMA flow diagram, Figure two). No additional studies were identified by hand-searching three relevant Cochrane reviews [209-211].

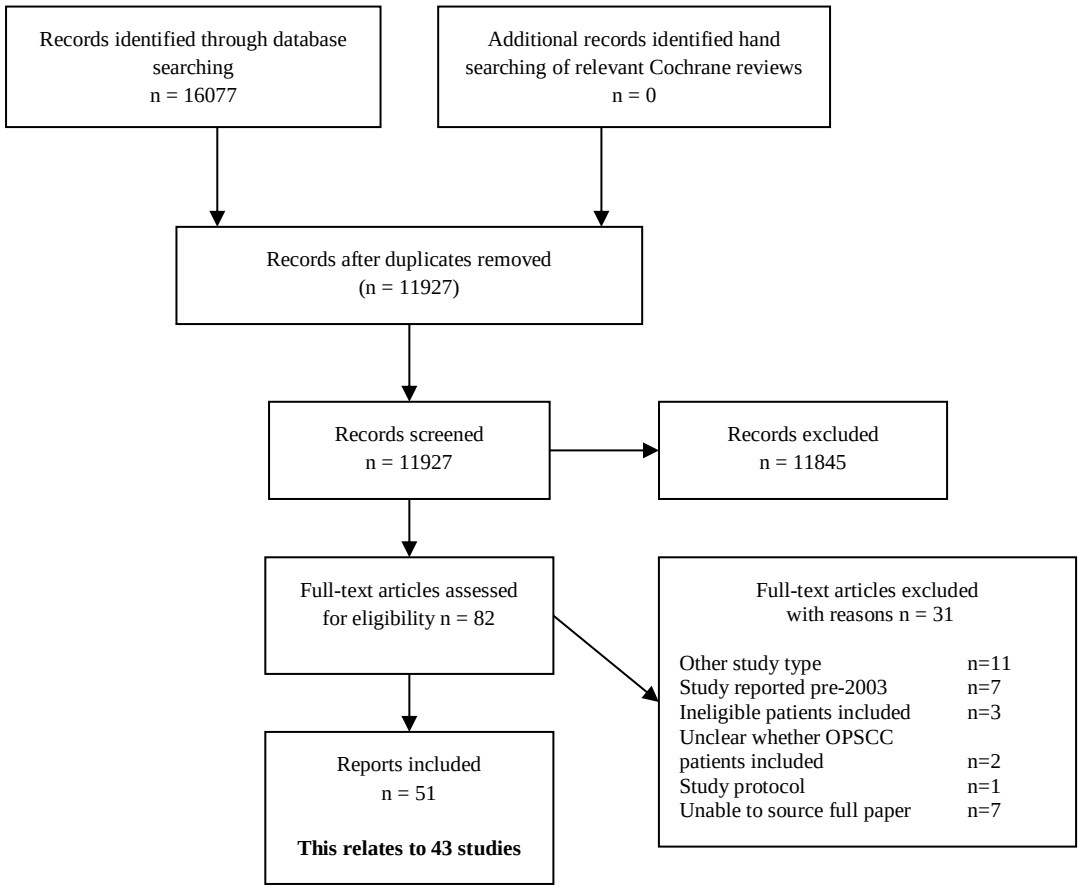


Figure 2. PRISMA flow diagram, identification of studies

2.4.1.1 Exclusion of studies

Phase I - exclusion by title

Due to the large number of studies (n=11,245) excluded at title review we did not individually categorise by reason for exclusion. The main reasons for exclusion were however:

- Non-SCCHN/OPSCC studies
- Ineligible study design e.g. case report, editorial or early phase RCT
- RCTs of interventions for the management of side-effects of treatment

Phase II – exclusion by abstract

In phase II, a further 600 studies were excluded. A large number of foreign language studies and conference abstracts were identified and published work was searched for using PubMed and the clinical trials registry, www.clinicaltrials.gov.

Phase III – exclusion at full paper review

At this point we were able to identify all eligible phase III RCTs and those studies to which a number of published papers related. Excluded studies were mainly SCCHN trials that did not feature OPSCC patients, RCTs of interventions for the management of side-effects of treatment, treatments for patients with metastatic or recurrent disease and subsequent published work relating to trials reported and published prior to the eligibility time frame (1st January 2003 – 14th May 2013) e.g. long-term follow up reports.

Of the 82 studies fully reviewed, 51 were eligible. These related to 43 individual RCTs. Of the 31 excluded studies, 11 were another study type, 7 were long term results for studies that had been reported before 1st January 2003, 2 did not clearly

state whether they included oropharynx patients, 2 included patients with metastatic or recurrent disease, 1 study included a 17-year-old patient and 1 was a reference to a study protocol which wasn't published. We were unable to source full papers for 7 studies (see figure 2).

2.4.1.2 Intra- and inter-rater agreement

A random sample of 50 excluded titles were identified. Their abstracts were reviewed by AW, and one study was identified that should have been included for full paper review. A further 50 abstracts were reviewed and no further studies were identified. A second reviewer (LW) assessed full papers for 40 of the excluded titles, to check for accuracy of exclusion. There was 100% agreement that the identified papers were ineligible. A further clinician reviewer (KL) and the senior authors (TMJ and CTS) reviewed a random sample of 20 of the identified studies to judge at what stage they would have included or excluded them. Whilst there were disparities in the stages at which the different authors would have excluded studies, this wouldn't have had an impact on the final studies included as when full papers were reviewed there was 100% agreement. The senior authors (TMJ and CTS) reviewed studies about which there was uncertainty.

2.4.2 Outcomes extraction

The study team agreed to extract all outcomes either specified in the methods or reported in the results whether or not they were listed as study endpoints.

2.4.3 Description of the included studies

The 51 included reports related to 43 individual RCTs. Additional publications arising from the studies are outlined below. These reported quality of life, additional analyses and long-term follow up data for trials reported in the review

time frame. Appendix three presents the characteristics of all the included studies and the outcomes they reported. Table one shows the additional reports for the included studies.

Papers	Study
Smid, 2003	Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma
Zakotnik, 2007	Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin
Cooper, 2004	Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck
Cooper, 2012	Long-term follow-up of the RTOG 9501/intergroup phase III trial: Postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck
Huguenin, 2004	Concomitant cisplatin significantly improves loco-regional control in advanced head and neck cancers treated with hyperfractionated radiotherapy
Ghadjar, 2012	Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94)
Bonner, 2006	Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck
Curran, 2007	Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab
Bonner, 2010	Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival
Vermorken, 2007	Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer
Van Herpen, 2010	Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323)
Ackerstaff, 2009	First-year quality of life assessment of an intra-arterial (RADPLAT) versus intravenous chemoradiation phase III trial
Rasch, 2010	Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial
Ackerstaff, 2012	Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer

Table 1. Additional reports for included studies

2.4.3.1 Participants

In total, 10,951 patients were randomized, 5286 (48.3%) had OPSCC. Additional subsites included oral cavity (30 studies), hypopharynx (38 studies), larynx (34 studies), unknown primary (2 studies), nasopharynx (3 studies) and paranasal sinuses (2 studies). Two studies included 'other' subsites, not specified [212, 213]. Only 2 studies recruited OPSCC patients exclusively [214, 215].

2.4.3.2 Interventions

Interventions are shown in table two. There were 5 trials of radiotherapy alone, 27 trials of chemotherapy and radiotherapy, 9 trials of surgery and chemotherapy and/or radiotherapy, 1 trial of radiotherapy and the Epidermal Growth Factor Receptor antagonist, Cetuximab (Erbitux®) and 1 trial of radiotherapy plus Carbogen breathing. No surgery only RCTs were identified.

Intervention(s)	Number of trials (%)	Number of patients (%)
Radiotherapy and chemotherapy	27 (62.7)	6888 (62.9)
Surgery +/- radiotherapy +/- chemotherapy	9 (20.9)	1791 (16.3)
Radiotherapy alone	5 (11.6)	1747 (16.0)
Radiotherapy and Cetuximab (Erbitux®)	1 (2.3)	424 (3.9)
Radiotherapy and Carbogen breathing	1 (2.3)	101 (0.9)
Total	43	10951

Table 2. Interventions in the included studies

2.4.3.3 Centres

The cohort included 12 single centre and 26 multi-centre studies (range 2-82). A number of studies were conducted by national and international collaboratives, namely the Eastern Cooperative Oncology Group (ECOG), Southwest Oncology

Group (SWOG), Radiation Therapy Oncology Group (RTOG), Trans-Tasman Radiation Oncology Group (TROG), Multicentre Hellenic Cooperative Oncology Group, Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) and the European Organisation for Research and Treatment of Cancer (EORTC). From the published report, it was not possible to identify the number of centres for 5 studies arising from Cuba, India, Singapore and the USA [216-220].

2.4.4 Powering of studies

Thirty-four studies reported a sample size calculation, with 50% of these recruiting to target. Studies that did not report a sample size calculation were more likely to recruit fewer patients. The median number of recruits to non-powered studies was 72, (IQR 60 to 106) and to powered studies, 247 (IQR 132 to 381).

2.4.5 Number of outcomes measured

Initial screening identified 77 verbatim outcomes. Ten of these were defined by the time at measurement. As we wished to establish *what* was measured rather than *when* it was measured, we categorised these outcomes, excluding time-points such that three- and five-year loco-regional control were absorbed into 'loco-regional control'. Synthesis of outcomes, excluding time-points reduced the number of outcomes to 67. I reviewed the definitions of the outcomes in each study, and the ways in which the outcomes were measured. This process and the outcomes synthesis was cross-checked by the rest of the study team (TMJ, CTS and BY).

Nine different verbatim terms had the same definitions or were measured in the same way and could feasibly be categorised as the same outcome (see table three), therefore a total of 58 distinct outcomes were identified in the 43 included studies with a total of 259 outcomes measured across all studies and a mean number of 6

outcomes per study (range 2 to 12). The list of 58 outcomes is shown in appendix four.

2.4.6 Outcome definitions

Only 6 studies (14%) provided a definition of every outcome in the trial and 2 studies failed to define any of the outcomes. Of all outcomes, 58.3% (151/259) were defined. Overall survival was defined in 46% (18/39) of studies, either as survival from randomisation or from the start of treatment. In different settings the time from randomisation to starting treatment will vary, and it is difficult to say how much heterogeneity this introduces as this information was not published in any of the studies. Some studies censored patients at the last known follow-up, others didn't state how patients were censored. Loco-regional control was only defined in 7 of the 18 studies (38.9%) that measured it. In 5 of these studies loco-regional control was the primary outcome. Important differences were observed in how loco-regional control was defined. Most studies considered loco-regional *recurrence* of tumour to signify an event for loco-regional control, whereas Grau et al. defined loco-regional relapse as any *persistent or recurrent* disease. In all other definitions loco-regional failure was defined by disease recurrence, not persistence. Their definition would represent two different outcomes; loco-regional control and progression-free survival. By this definition, patients who were never tumour free were not censored. Zackrisson et al. [221] were careful to point out that patients who were never tumour free were censored at time-point '0' for loco-regional control, because they never had loco-regional control.

Verbatim term	Outcome domain
Adverse event	Acute toxicity
Early normal tissue reactions	
Incidence of major and minor complications	
Late normal tissue reactions	Late toxicity
Local relapse-free survival	Local recurrence-free survival
Tumour response	Response
Overall response rate	
Time to local or nodal treatment failure	Time to loco-regional failure
Duration of loco-regional control	Loco-regional control

Table 3. Outcome domains

2.4.7 Outcomes in the included studies

The most commonly measured outcomes were acute toxicity, overall survival and late toxicity, measured in 100%, 90.7% and 69.8% of the included studies respectively. These were the only outcomes reported in more than 50% of the studies. Even then, acute toxicity was only specified as a primary or secondary end point in 60.5% (26/43) of studies. Thirty-four outcomes were each only measured

in a single study, therefore less than half of the outcomes (24/58, 41.4%) were measured in more than one study. Only 7 RCTs, all published after 2006, measured health-related quality of life (HR-QOL). This was often reported in separate publications from the main study report, and, in some studies, conducted longitudinally over a number of years [222, 223]. The ten most commonly pre-specified or reported outcomes are shown in table four.

Outcome	Number of studies (%)
Acute toxicity	43 (100.0)
Overall Survival	39 (90.7)
Late toxicity	30 (69.8)
Loco-regional control	18 (41.9)
Response	16 (37.2)
Disease-free survival	14 (32.6)
Progression-free survival	10 (23.3)
HR-QOL	7 (16.3)
Distant metastases	6 (14.0)
Local control	5 (11.6)

Table 4. The ten most commonly reported outcomes

2.4.7.1 Primary outcomes

The primary outcome was clearly stated in 34 studies, deduced from the sample size calculation in 3 studies, deduced from the text in 3 studies and unclear in 3 studies. The most common primary outcomes were loco-regional control (12 studies), overall survival (7 studies), progression-free survival (3 studies), disease-free survival (3 studies) and loco-regional recurrence-free survival (2 studies). Six studies stated more than one primary outcome. Some functional outcomes are

routinely measured using toxicity criteria; however studies are rarely powered on these. This review identified only two studies powered on functional outcomes; Nutting et al, 2011 which was powered on Xerostomia at 12 months according to the Late Effects of Normal Tissues Subjective-Objective Management Analytic (LENT SOMA) and Gupta et al which was powered on acute salivary gland toxicity (grade 2 or greater) measured according to the Radiation Therapy Oncology Group (RTOG) acute salivary gland toxicity criteria [224, 225].

2.4.7.2 Types of outcomes

Survival outcomes included overall survival, cancer-specific survival and failure or progression-free survival. These were measured and analysed as time-to-event outcomes. Outcomes related to disease control, including response, progression or recurrence were measured radiologically or by clinical assessment. Disease control was either measured as response rate at a particular point in time or, like survival, as a time-to-event outcome e.g. time to progression or loco-regional failure. Loco-regional control was the most commonly used outcome to assess disease response.

Adverse events are routinely measured as a requirement of safety reporting, and were measured in all of the included studies, but specified as outcomes in only 60.5% of trials. Acute toxicity was measured and reported using a validated composite outcome tool in 35 of the 43 studies. In 8 studies acute toxicity was measured but it was unclear whether a validated tool was used. Acute toxicities were predominantly measured using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria (20 out of 36 studies) for radiation and the US National Cancer Institute Common Toxicity Criteria for chemotherapy (14 out of 33 studies). These are observer reported outcome instruments. No single study reported all of the toxicities. It is unclear whether this is because many of the toxicities were not experienced or whether they were measured but just not reported. Late toxicity was measured less consistently, with

13 studies not reporting any late morbidity data. The RTOG/EORTC late morbidity criteria was the most commonly used measure of late toxicity, used in 24 studies. No methods were employed to specifically measure surgical morbidity.

Health-related quality of life was assessed using a number of different patient reported outcome measures. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30) and Head and Neck Module (EORTC QLQ-H&N35) were used in 6 of 7 studies, although the questionnaires were not always completed in their entirety, and not for all patients, even for baseline or early assessment and, as expected, attrition increased with time. The Functional Assessment of Cancer Therapy (FACT) - Head and Neck Symptom Index was used in one study. All studies measured HR-QOL longitudinally, over varying periods of time. At baseline, Curran et al [226] collected data for 419 of 424 patients, van Herpen et al [227] for 353 of 358, Ackerstaff et al [228] for all 207 patients, Zackrisson et al [221] for 683 of 733 patients, Rischin et al for 836 of 853 and Rodriguez et al [216] for only 42 of 106 patients. Nutting et al [224] only reported numbers for xerostomia assessment, being 39 of 94 at baseline and 12 months and 33 of 94 at baseline and 24 months, this was contrasted with 73 of 94 patients having reportable data for the primary endpoint at 12 months and 55 at 24 months. HR-QOL outcomes were not collected as consistently as clinical outcomes. In addition to the problems identified in this review with missing assessments, incomplete PROMs are also a methodological concern that cause problems with the statistical assessment and interpretation of PROM data from a trial [229, 230]. Ackerstaff et al [222, 228] explicitly stated that only selected questions from EORTC-QLQ C30 and EORTC QLQ-H&N35 were used, in addition they used a trial specific questionnaire. Selective use of HR-QOL questionnaires like this makes statistical analysis difficult and is a methodological concern, and a potential source of bias [229, 230]. Zackrisson et al used average score imputation to replace missing scores in HR-QOL questionnaires, allowing questionnaires with up to a third of the answers

missing [221]. This is a commonly used method for accounting for missing scores [231], a particular problem when such questionnaires are completed by patients remotely [232]. In most cases, baseline questionnaires were completed at the point of randomisation or prior to starting treatment. No studies specified whether patients completed baseline questionnaires themselves or with a clinician, in most cases however subsequent questionnaires were posted out to patients to be completed at home, so it is assumed these were completed by patients without the assistance of a clinician.

2.4.8 Comprehensive outcomes list

Fifty of the 58 outcomes could be categorised under broader constructs known as 'outcome domains' relating to toxicity (10 outcomes), survival (16 outcomes), disease control (23 outcomes), and health-related quality of life (1 outcome). These domains were not determined a priori but rather upon analysis of all of the identified outcomes. They were categorised independently by AW and then the study team (TMJ, CTS, BY). The remaining eight outcomes were not taken forward to the comprehensive outcomes list as they were trial specific, not repeatable, or not technically outcomes of treatment. Non-categorised outcomes were 1) Identification of parameters that might predict a benefit from carbogen breathing 2) Immunogenicity 3) Influence of variations in dose–volume distributions in targets and critical organ volumes on the outcome regarding both disease and morbidity 4) Pathological response 5) Patterns of failure 6) Prognostic factors 7) Time to radical surgery 8) Variations in outcome in different sub-sites and stages with respect to treatment type.

2.5 Discussion

2.5.1 Key findings

The systematic review identified 58 distinct outcomes reported in 43 RCTs. Only three outcomes were measured in more than 50% of studies, and fewer than half of the outcomes (24/58, 41.4%) were measured in more than one study. Therefore, more than half of the outcomes could not be compared with results from comparable trials, or combined in a meta-analysis. This is a waste of researchers' time and effort, a waste of research funding and, above all, unethical if patients are subjected to repeat testing that will have little added value.

In the studies included in this review, definitions were only provided for 58.3% of the outcomes measured, with only 6 studies (14%) defining all reported outcomes. This could lead to the erroneous synthesis of differing outcomes in meta-analyses if verbatim terms are taken for granted as measuring the same events. Cause-specific survival was defined by Cooper et al. as 'death due to the study cancer' but by Haffty et al. as 'those deaths that occurred with recurrent disease or as a result of recurrent disease' [66, 219]. These outcomes are given the same name but could be measuring different events; Cooper et al might consider death following progression of the cancer whereas Haffty et al appear to only consider recurrent disease – not progression. Two further studies measured cause-specific survival but did not define it [221, 233]. Conversely, it is likely that studies measured outcomes with different verbatim terms in the same way, however lack of definitions or any form of standardised nomenclature makes this assessment difficult.

This problem has been identified in clinical trials in other areas of healthcare, leading to calls for standardised definitions of efficacy endpoints. In a review of a selection of the most recently published clinical trials of aromatase inhibitors in breast cancer by Hudis et al. [234], disease-free survival (DFS) - a commonly used surrogate endpoint in OPSCC clinical trials - was found to be defined differently

between trials, with different events included in its definition between trials. Additionally, individual events were found to have been inconsistently defined, compounding the variability in its definition between trials. This raises the possibility that a treatment may be declared as resulting in improved DFS as defined one way, but not when defined differently. These findings prompted a drive for Standardised Definitions for Efficacy End Points in adjuvant breast cancer trials (The STEEP system); endpoint definitions that identify the component events that comprise the endpoint and define each component event.

This is not the only such initiative. The National Cancer Institute (NCI) developed the Common Data Elements (CDE) to serve as a controlled vocabulary of data descriptors for cancer research [235]. This sits within the broader resource portal of the US National Institutes of Health (NIH) (http://www.nlm.nih.gov/cde/). This may be consulted to identify end points with standardised definitions for use in clinical trials, or for data elements to be collected by future studies. Some studies have sought to identify CDEs alongside COS development for specific clinical conditions, as the two complement one another, increasing the homogeneity and consistency of outcome measurement and reporting thus facilitating cross-study comparisons or synthesis [236]. COSMIN use consensus methods to agree on the taxonomy, terminology and definition of outcomes [237] and this process will need to be applied to our COS to improve and refine outcome measurement in clinical trials in OPSCC.

The review demonstrated that outcome selection in contemporary OPSCC RCTs is focused on disease control and survival, with little attention in many cases given to the assessment of functional outcomes and HR-QOL. These findings were consistent with previous systematic reviews of OPSCC RCTs which have demonstrated inconsistent reporting of HR-QOL and incomplete reporting of adverse events [169-171, 238]. In 1981, the World Health Organisation (WHO) made recommendations that a measure of patients' emotional well-being should be

made in clinical trials in oncology [239]. Despite this, and despite the well-known effects of treatment for head and neck cancer on quality of life, this was only reported in 7 trials in this review, all published after 2006. Jensen et al. [240] demonstrated strong correlation between treatment-related toxicity and HR-QOL in head and neck cancer patients, yet, as described below, adverse effects were also incompletely reported.

Acute toxicities of treatment were universally measured, but rarely completely reported. Validated, standardised criteria were commonly used for the assessment of toxicities however trial reports generally failed to report more than a few of the outcomes. Whilst it is assumed that this is due to word count limits, it is not known whether studies selectively measured or selectively reported the outcomes or whether the events simply didn't happen. It is now possible for evidence such as this to be made available online, as reported by Rischin et al, 2010 [223]. This was the only study to report all acute toxicities.

Late toxicities were less frequently measured than acute toxicities, and therefore less is known about these late effects of treatment. Thirteen studies failed to report any late toxicity data. Acute toxicities were measured at similar time-points during and immediately after treatment, time-points for measurement of late effects were far more variable, and these were often not measured for more than two years beyond the end of treatment. Also, because mortality is relatively high, the number of patients or events for late effects may be small. Consideration of late effects is, however, of paramount importance in younger, HPV-positive OPSCC patients who will live for a long time with the adverse effects of treatment. Where equipoise exists for survival, the incidence and severity of such adverse effects, long-term dysfunction and health-related quality of life are likely to be important to clinicians when making treatment recommendations, and for patients when making treatment decisions [46]. Efforts must therefore be made to ensure that patients are followed

up for longer time periods to establish the trajectory of adverse events, which are likely to inform future treatment strategies, health-care decision making and policy.

2.5.2 Conclusion

The consistency with which clinical and patient-reported outcomes are measured in OPSCC RCTs is poor. Redundant outcomes may never contribute to a meta-analysis or influence clinical practice. The development and adoption of a minimum outcome reporting standard, such as a COS would significantly improve outcome reporting in trials, providing data to be compared and combined in meta-analyses. The list of outcomes identified in this systematic review will be used to develop a comprehensive outcomes list and questionnaire for the Delphi study described in chapter four, and ultimately to a COS for clinical trials in OPSCC. A unified discussion for the thesis is presented in chapter five.

Chapter 3

A qualitative study to identify outcomes of importance to patients and carers in clinical trials in oropharyngeal cancer

3.1 Rationale for this chapter

Oropharyngeal cancers and their treatments often have a profound effect on a person's quality of life, due to their impact on normal functioning [241]. It is often difficult for people to carry on their normal lives because of the combined effects of multi-modality therapy. For this reason, those close to someone being treated for OPSCC are often involved in their day to day care. For example, they may help with, or be entirely responsible for, meal preparation, self-care, physical mobility, medicines management and transport to and from hospital appointments. Furthermore, carers are often required to manage illness-related symptoms, make care decisions, respond to emergencies and provide emotional support [242]. Due to these demands, a head and neck cancer diagnosis has significant consequences for the quality of life of the carer, as well as the patient [243]. Patients have real, experiential knowledge of what it is like to have OPSCC and go through treatment, and carers are first-hand or 'involved witnesses' to this [194]. With different perspectives, both are experts in the lived experience of a cancer diagnosis and treatment, and therefore have much to contribute to research in this area.

In a qualitative study, Hubbard et al. explored the role of the carer in decision-making in cancer care [244]. In some circumstances, patients found it difficult to process information, and on occasions, carers acted as a conduit for information. In this sense, the carer can contribute to moving the patient from a relatively passive position in the process to one where they have a greater degree of input and knowledge exchange in relation to treatment decision-making. Carers can also play a role in eliciting information from clinicians so that the patient is more informed

during the consultation. At times, when it may be difficult for the patient to engage in discussion, the carer may be able to pre-empt what information the patient would like to receive, judging the quantity and type of information that the patient needs. Thus, the carer can play a role in not only directing information flow but also in deciding on the amount and type of information. The carer therefore provides a unique perspective on the factors that influence patient decision making regarding treatment, and therefore on which outcomes they prioritise.

The emergence of HPV-related OPSCC in a younger patient cohort with greater odds of survival, draws more focus to the long-term sequelae of treatment [10]. The desire to establish whether contemporary treatment strategies can be de-escalated to reduce treatment related morbidity whilst preserving survival underpins much of the current research in OPSCC [10, 245]. Whilst research in laryngeal cancer has shown that some patients will accept reduced odds of survival in favour of laryngeal preservation [246-250], acceptable trade-offs have not been established for OPSCC [47]. There is therefore an urgent need to establish outcome priorities for these patients, particularly in the HPV-positive cohort.

As discussed in the introduction to this thesis, canvassing patient opinion is a key step in COS development, as there is good evidence that healthcare professionals do not always know which outcomes are most important to patients [251, 252] or may prioritise outcomes differently [252, 253]. Research may contribute little to the evidence base if it does not measure outcomes that are clinically important and patient relevant. There are many ways in which patients can be involved in COS development, and in this study we decided to involve patients in the identification of outcomes of importance and in the consensus exercise to ratify the contents of the COS.

Qualitative interviews were employed to identify outcomes of importance to patients at the suggestion of a patient and carer research forum in Liverpool who

we consulted on study design. From clinical experience, and our knowledge that outcomes related to functioning and quality of life were likely to be highly important to patients, we proposed involving patients in some form of qualitative inquiry – possibly a focus group. Patients and carers felt that the privacy of one-to-one interviews would be easier for the research subjects as this would be a highly emotive topic for many people to talk about, and open discussion may be stifled in a group setting. Furthermore they suggested that interviewing patients and carers together may not work for some couples as their experiences could have led to changes in the nature of their relationship, the balance of power and at times to conflict, all of which may have caused them to hold back in the interview.

I therefore decided to use one-to-one qualitative interviews with patients and carers to elicit opinions about outcomes of importance, and to try to understand how outcomes relating to functioning and quality of life sat alongside 'harder' clinical outcomes such as survival. I also wished to investigate whether patients with HPV-positive disease prioritised different outcomes. Due to available resources, I chose to undertake the interviews myself. In choosing to do so it was important to be reflexive about my role, and the influence of my position, beliefs and behaviours on the research process. My own reflections on this are presented later in this chapter.

3.2 Objectives

The objectives of this qualitative study were to:

1. Identify which outcomes are important to patients and their carers

2. Ensure that the comprehensive list of outcomes developed for the Delphi study does not overlook outcomes of importance to patients

3. Identify the language used to describe outcomes to facilitate the development of the Delphi consensus survey

3.3 Methods

I conducted a series of semi-structured interviews with patients treated for OSPCC and their carers between March and October 2013, in the UK and the US. I will present the methods employed to identify their outcomes of importance in the context of clinical trials, and the results of this enquiry.

3.3.1 Setting

Patients were recruited from head and neck cancer survivorship clinics. Three centres were used for recruitment; NHS hospitals in Liverpool and Sunderland, UK and The University of Texas MD Anderson Cancer Center, Houston, Texas.

The three treatment centres differ by primary treatment modality and patient socio-economic status; patients with locally advanced OPSCC in Liverpool are largely offered transoral laser microsurgery (TLM) and adjuvant radiotherapy and those in Sunderland and MDACC primary chemoradiotherapy, which is considered the current standard of care. Socio-economic status has a significant impact upon outcomes in SCCHN and broadly speaking, MDACC patients are of higher socio-economic status because of the system of healthcare funding in the US and the costs of treatment at that particular centre. It was hypothesised that increasing the diversity of our patient sample would add to the richness of the data collected and the breadth of both the perspectives and the transferability of the findings.

3.3.2 Participant eligibility

Inclusion criteria

- Patients: Adults, over the age of 18, who were up to 5 years following completion of treatment for OPSCC

- Carers: An individual, such as a spouse or family member, who provides informal care to the patient

Exclusion criteria

- Patients with active disease were excluded because the window of opportunity to interview them prior to commencing treatment would be very short and we did not believe it to be ethical to interview patients going through treatment
- Patients with known or suspected recurrence were excluded because we felt the anxieties and concerns associated with this state would skew outcome priorities
- Non-English speakers

3.3.3 Recruitment process

Recruitment methods differed between the three centres and are discussed below.

Liverpool
(Aintree University Hospital NHS Foundation Trust, Royal Liverpool and Broadgreen University Hospitals NHS Trust and St Helens and Knowsley Teaching Hospitals NHS Trust)
Outpatient clinic lists and case notes were scrutinised by local research staff to identify eligible patients, attending for routine cancer follow up. The patients' treating clinician approached them to ask if they would participate in the study at

the end of their outpatient appointment. If they were interested, AW or local research staff then discussed the study in more detail. If the patient's spouse was present they were asked to participate. Potential participants were given an information leaflet and called after five days by AW to ask if they would like to participate. Arrangements were made for the interview if the patient provided verbal consent.

City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK

Outpatient clinic lists were scrutinised by JMP, a speech and language therapist, to identify eligible patients attending for routine cancer follow up. They were contacted by telephone by JMP to discuss the study. If they were interested they were posted an information leaflet and contacted by AW after five days to discuss the study in further detail and if verbal consent was provided, make arrangements for the interview.

The University of Texas MD Anderson Cancer Center, Houston, Texas

MP, a data analyst at MDACC screened case notes for eligible patients in upcoming surveillance clinics. Eligible patients were invited to participate by letter, sent at least 14 days before their appointment. This described the study and asked patients to call a secure line at MDACC to schedule an interview during their next visit, should they wish to participate. AW then called patients and, using a telephone script (Appendix five), provided further information about the study and confirmed verbal consent to participate.

3.3.4 Participant sample

Patients were sampled with the aim of achieving diversity for certain clinical, social and demographic characteristics that we thought may influence their experiences, their perceptions of their experiences and their priorities. These are

discussed later in the chapter. Carers of recruited patients were sampled by convenience.

There is a certain temptation in qualitative research to sample patients who will 'perform' well at interview; that are known to have strong opinions or offer interesting insights into the condition; I met several patients like this involved in the patient research collaborative who were keen to be interviewed for the study, and whom I know would have provided good 'soundbites'. It was felt however that their perspectives might be atypical compared to other patients because of their experiences with clinical trials and relationships with healthcare professionals.

In purposive sampling, participants are selected because they meet the criteria anticipated by the researcher as being relevant to the research question. This process was facilitated by a sampling matrix. Initially, patients' characteristics were recorded against this matrix, and subsequent attempts were made to identify patients with characteristics not yet identified in the patient sample, to 'fill the gaps' (see table five). That is, patients were initially approached consecutively, by convenience sampling, to reduce the risk of inadvertent researcher sampling bias, and, latterly purposively sampled, to increase the diversity of our participant sample [2].

	Treatment Modality											
	Surgery/TLM + PORT						CRT					
	Months since treatment						Months since treatment					
	0-24		25-48		49-60		0-24		25-48		49-60	
Age Group	M	F	M	F	M	F	M	F	M	F	M	F
18-40												
41-60												
61-100												

Table 5. Sampling matrix for patient recruitment

(CRT=chemoradiotherapy; F=female; M=male; PORT= post-operative radiotherapy; TLM=transoral laser microsurgery)

Eligible patients were identified by case note review, and once verbal consent was provided by patients, AW reviewed case notes in order to collect demographic and

clinical data. The patient's age, gender, co-morbidities, tumour site and stage, treatment modality and length of time post-treatment were recorded. HPV status was recorded as we anticipated that this may influence outcomes prioritised by patients and carers, however this was not a variable in our sampling matrix as we knew this information would not be available for patients treated prior to routine testing for HPV. Socio-economic status was estimated via the Index of Multiple Deprivation (IMD) in the UK and by educational level in the US.

We know that culture and patient values are important factors that may affect decision making and how treatment and recovery are negotiated [254]. Significant efforts were made to recruit ethnic minority participants, however none were available in the study time frame in the UK and none responded to invitations to attend for interview in the US.

Based on work by Guest et al [3] we anticipated that we would need to interview around 30 patients and carers in total to reach a point of theoretical saturation, that is, the point at which no new conceptual insights would be generated through further interviews [255]. Thus, we aimed to recruit 10-15 participants per site. Our sampling began in Liverpool, and ongoing analysis of the data from this site was used to inform recruitment at subsequent sites.

3.3.5 Interview setting and format

In the UK, interviews were conducted in patients' homes. In the US because most patients did not live near MDACC, we interviewed them in the outpatient clinic when they were attending for follow-up. We endeavoured to interview MDACC patients after follow-up appointments as anxiety about recurrence was likely to be elevated beforehand, which may have biased the reporting of outcomes [193].

A semi-structured interview format was used, comprising open ended questions that defined the area to be explored. This allows the interviewer or interviewee to diverge from the questions or prompts in order to pursue an idea in more detail [256]. Such an approach facilitates focused yet conversational interactions, and this was felt to be particularly appropriate for this group of patients and for the objectives of this study, as it allows the interviewee to set the agenda and therefore potentially identify previously unanticipated outcomes. Additionally, because of the morbidity associated with treatments, interviews were expected to be somewhat emotionally charged, and it was hypothesised that a more conversational approach would allow me the flexibility to show empathy and explore these issues without having to strictly adhere to a list of questions, required by more structured methods of inquiry.

We requested to interview the patient and carer separately to avoid the difficulties of interpreting individual experiences from data collected at joint interviews, whereby it would be necessary to interpret the accounts of each party in the context of how it is shaped by the presence of the other party, however, where participants expressed a preference to be interviewed together I agreed to this [257].

3.3.6 Data collection methods

Topic guides were developed by BY and myself, reviewed by the Mersey Head and Neck Cancer Patient and Carer Research Forum and piloted by Heather Bagley, the COMET PPI co-ordinator. These guided the discussions and ensured comparability between interviews (Appendix six). Different topic guides were developed for patients and carers. These were developed iteratively over the course of the study, with some questions removed and some added in light of the ongoing analysis. Certain questions were re-worded if they were found to be unclear to patients, and some removed altogether if they did not generate any useful data. Some questions were added to probe interesting themes that arose during the

course of the interviews. Field notes were made after each interview to record observations about the interviewee(s), environment and initial thoughts and analysis. These were triangulated with the transcripts and interview notes during my analysis.

The remit of the interviews was to identify outcomes of importance to patients. Rather than engage in a discourse about research and clinical trials, which would be unfamiliar to most and to minimise the risk of obtaining generalised or idealised accounts, interviews initially focused on participants' experiences of tangible aspects of their current day-to-day lives, activities and pastimes before exploring their opinions and reflections on how their lives and priorities have changed since their treatment.

At the end of each interview I summarised the main problems or priorities of interviewees as a form of respondent validation. I asked them to prioritise the outcomes mentioned during the interview, and to consider which outcomes would help them to differentiate between treatments if there was equipoise for survival. Whilst the interviews were conversational in nature, discussion was progressively directed towards identifying priority outcomes. Patient and carer pairs, interviewed separately, would occasionally contradict one another however I did not draw attention to these discrepancies to preserve confidentiality.

3.3.7 Data processing

Interviews were audio-recorded. In the UK, audio-recordings were downloaded to a secure drive at the University of Liverpool. I personally transcribed the first three interviews verbatim, including any ‘erms’, ‘errs’, ‘hmmmms’, moments of hesitancy, affectations and utterances. A professional transcription agency was used to make subsequent transcriptions and I provided the agency with a protocol

specifying the document formatting and exact level of transcription required. I reviewed all transcripts to ensure their accuracy and make necessary corrections.

It is not possible to anonymise transcripts from semi-structured interviews because the combination of circumstances and events could still be recognised by the interviewee or someone familiar to them, the transcripts were therefore 'pseudonymised'. In this process the names of places and people are removed, along with dates or other unique patient identifiable data. Once transcribed and pseudonymised, interviews were deleted from the audio-recorder. I transcribed and pseudonymised all US interviews, these were then emailed securely to me on my return to the UK.

3.3.8 Data analysis

The first four interviews were coded independently by BY and myself. We then met to discuss our coding framework and analysis. The codes identified were consistent and therefore subsequent interviews were only coded by me. An audit trail was kept of my analysis and the subsequent changes to the interview topic guides.

As a theoretical framework, I drew on the principles of grounded theory [4]. This inductive approach involves identifying analytical categories from the data rather than defining them a priori. I felt this to be the most suitable approach for this study in which I was keen to avoid making assumptions about outcomes of importance, because of my clinical experience. Initial content analysis allowed me to identify the outcomes and language used to describe them in order to develop my comprehensive outcomes list. Subsequent analysis was more interpretive and informed by the principles of the constant comparative method, with several procedural steps to ensure its quality [258]. I used open coding to identify the concepts and categories in the data which formed the basic units of analysis. I then

used axial coding to confirm that the concepts and categories I had induced from the data were accurate and explored these concepts and how they were related. I wished to understand whether there were nuances in the patient sub-groups (i.e. older vs younger; HPV-positive vs HPV-negative; treatment modality) that affected the outcomes of importance and hoped that such an approach would shed light on these differences. The language used by patients was helpful for adapting my questioning style as the interviews progressed, and I often probed themes using terms used by other patients.

Initially, I read each transcript several times before developing open codes to describe each relevant unit of meaning. Initial open coding occurred at multiple levels, from detailed descriptions of experiences line by line, to the general stance participants took towards different aspects of their lives. Through comparison within and across the transcripts, the open codes were gradually developed into theoretical categories and subcategories to reflect and test the developing analysis.

The categories were organised into a framework to code and index the transcripts using Excel software. The framework categories were continually checked and modified to ensure an adequate 'fit' with the data, whilst also accounting for variant or exceptional cases. The categories and the assignment of data to them was reviewed by a second member of the project team (BY).

The analysis of patients' and carers' accounts initially proceeded in parallel but related, courses. That is, I first analysed data within each group for common themes, such as what was important to patients and carers and how their lives had been affected by their illness and treatment [259]. As the analysis developed I compared across the different groups to identify convergences and divergences. I examined how participants presented their accounts as well as the content of the interviews; I did not simply take participants' accounts at face value. This was important because many of the issues discussed were emotive and I expected a

certain amount of stoicism and underplaying of the importance of events in this sample.

Finally, I compared data across the different groups (gender, age, HPV status, treatment modality and socioeconomic status) and analysed for recurrent patterns in how these characteristics shaped participants' priorities. I kept field notes to systematically record the contextual details of the interviews and the evolution of the analysis. I lead a process of 'cycling' between the developing analysis and new data, and the study team (BY, CTS, TMJ) 'tested' the analysis by periodic discussion of transcripts and my analysis.

3.3.9 Ensuring quality

Systematic, rigorous, and auditable analytical processes are among the most significant factors distinguishing good quality, from poor quality research [6]. There has been a move in recent years towards the use of 'checklists' to ensure that the reporting of qualitative research meets these requirements. Adherence to these reporting guidelines does not, however, guarantee quality. The uncritical and overly prescriptive adoption of such 'technical fixes' whilst appealing, achieves little unless they are embedded in a broader understanding of the principles of qualitative research [7].

As the interviewer, reflecting on one's own personal characteristics and how these influence the data improves the credibility of the findings by allowing readers to assess how these factors might have influenced your observations and interpretations. One's own relationship with the patient and how they may perceive your position should also be stated [8]. I have reflected upon these factors in section 3.2.

I have made judicious use of reporting guidelines in this study, namely the Standards for Reporting Qualitative Research (SRQR) [9] and the Consolidated Criteria for Reporting Qualitative Studies (COREQ) [10] as recommended by the EQUATOR network.

I have endeavoured to demonstrate my analytical process, such that the conclusions reached can be traced back to open codes arising from the data (See example in appendix seven).

3.3.10 Patient and public involvement

Prior to seeking ethical approval for this study, the patient and carer information sheets were reviewed by Heather Bagley, the COMET PPI co-ordinator, for suitability of language and clarity of description of the research objectives (Appendix eight).

The interview protocol, patient and carer consent forms, information leaflets and topic guides were subsequently presented to and reviewed by the Mersey Head and Neck Cancer Patient and Carer Research Forum in Liverpool (http://www.hanc.org.uk/research.html). This forum is attended by patients who have been treated for SCCHN and their carers. As well as helping to ensure consideration is given to the views and interests of patients and carers when designing research projects, the forum provides advice on research proposals from a patient and carer perspective.

I sought general feedback from the forum on the study design and suitability of documentation, and more specifically regarding whether patients would prefer interviews or focus groups. The opinion was that because of the personal, and often emotional challenges faced by patients undergoing treatment, one to one interviews were likely to be more acceptable to patients. There was acknowledgment that

although those attending the forum were happy to discuss such issues in public, this view was not necessarily representative of the wider patient community. They suggested that a focus group could be conducted if it was felt that the interviews weren't fruitful.

Reflecting on my discussions with the group, the study team decided that rather than only including patients two to five years post-treatment we should extend this from immediately post-treatment up to five years post-treatment, as outcome priorities are likely to change over time, and will be different for each individual based on their own experience. Feedback from the group about wording and presentation was integrated into the protocol, patient and carer information sheets, topic guides and ethics application.

3.4 Governance, ethics and confidentiality

3.4.1 Research ethics committee and institutional review board approval

Ethical approval for this study was granted in the UK by the Liverpool Central Research Ethics Committee (reference 12/NW/0708). The study was registered on the NIHR portfolio, ID 13823 (17 January 2013).

Approval at MDACC (Houston, TX, US) was provided by the Institutional Review Board (IRB) (protocol number 2013-0285). The IRB was concerned about the potentially upsetting nature of the discussions that I would be having with patients, and a requirement of IRB approval was that a psychiatrist be available to counsel patients following interviews should I have concerns about a patient's psychological welfare.

3.4.2 Research and Development

In the UK, research and development (R&D) approval had to be sought for each individual trust in which we intended to recruit patients. This comprised three separate NHS Trusts in Liverpool, and one in Sunderland. The University of Liverpool was the sole sponsor for the study under the Department of Health's Research Governance Framework for Health and Social Care (2005).

Recruiting to 'theoretical saturation' meant that the exact number of participants required was difficult to specify in advance; this concept was relatively new to some R&D departments who were keen for prescribed recruitment targets and therefore questioned the methodological 'soundness' of this approach. These concerns were addressed by justifying the approximate sample size on the level of likely heterogeneity within the sample according to our sampling matrix (see table 5).

3.4.3 Data handling and storage

Identifiable participant information was defined according to the NHS code of practice on confidentiality (2003) and handled, processed and stored in compliance with the Data Protection Act (1998). This was stored separately to interview transcripts, consent forms, audio recordings and field notes. All identifiable participant data were encrypted and stored on the central university file store which is backed up daily. Hard copies were stored in a secure, locked filing cabinet at the University of Liverpool. A key linking identifiable patient information to the transcribed interviews was stored at Aintree University Hospital in Liverpool on the central research computer which is kept in a locked room.

It was a requirement of the Institutional Review Board (IRB) at MDACC that for information security, no identifiable patient information could leave MDACC.

Also, a requirement was that audio-recordings be transcribed internally. I therefore transcribed and pseudonymised the interviews personally and transcripts were sent to me securely on my return to the UK, and stored in compliance with the regulations as stated above. The protocol for data handling and storage described the procedures to be followed.

3.4.4 Consent

Verbal consent for the interviews was provided by patients when arrangements were made for the interview. Written, informed consent was requested on the day of the interview. In the UK, this was taken by me, and at MDACC by a member of permanent clinical staff, familiar with the study (see appendix nine). Participants were informed that they could withdraw consent up to the point of data analysis and they were asked whether they would like to see the published reports arising from the research.

3.4.5 Sources of funding

I was supported by the Medical Research Council (grant number G0800792) via the North West Hub for Trials Methodology Research. Additional travel grants were awarded by the British Association of Head & Neck Oncologists and The Royal Society of Medicine for grants to fund travel to Houston.

3.4.6 Data presentation

The analyses that follow are based on data from the 23 patients and 11 carers. Data extracts are indicated by quotation marks, along with the patient (C) and carer (CC) numerical codes. In the extracts, the ellipses (. . .) indicate omitted speech, double parentheses (()) enclose speech that was unclear, and brackets [ ] enclose text that was entered during transcription or analysis to replace names or aid interpretation.

Patients C1 - C9 were recruited in Liverpool, C10 - C15 in Sunderland and C16 – C23 at MDACC. Carers CC1 – CC6 were recruited in Liverpool CC7 – CC9 in Sunderland and CC10 – CC11 at MDACC.

The themes identified in my analysis that relate to outcomes of treatment are discussed below. The other themes identified are outside the scope of this thesis and will be discussed elsewhere.

3.5 Results

3.5.1 Participants

The face to face approach strategy used in the UK resulted in higher recruitment rates than those in the US done by letter. Compared to the 44 US patients who did not respond to the invitation letter, only four patients in the UK declined to participate after initial approach. Three gave no particular reason and one said he "wasn't one for talking about his feelings". In the US we did not have reasons for refusal. Table six shows the number of patients screened, approached and recruited. All carers that were approached participated in the interviews.

	Liverpool	Sunderland	MDACC
Screened	45	10	999
Eligible	11	8	67
Approached	11	8	52
Recruited	9	6	8
Carers	5	3	2

Table 6. Screening, approach and recruitment to interview

Thirty-one interviews were conducted with 23 patients (17 male and 6 female) and 11 carers (1 male and 10 female) between 1st March and 15th October 2013. Three of the patient-carer couples opted to be interviewed together, hence fewer

interviews than numbers of participants. Interviews with single participants lasted between 28 minutes and 2 hours 20 minutes; those with patient-carer couples lasted between 1 hour 36 minutes and 2 hours 32 minutes. Patient characteristics are shown in table seven, overleaf.

Patients		
Age (years)	**Median**	**Range**
	64	39-82
Sex	**Number**	**Percentage (%)**
Male	17	73.9
Female	6	26.1
Tumour stage		
Stage III	5	21.7
Stage IVA	17	69.6
Stage IVB	1	4.3
Oropharynx sub-site		
Glossopharyngeal sulcus	1	4.3
Soft palate	1	4.3
Tonsil	8	34.8
Base of tongue	13	56.5
HPV status		
Positive	10	43.5
Negative	6	26.1
Unknown	7	30.4
Treatment modality		
RT alone	1	8.7
CRT	7	30.4
TLM, RT + ND	9	43.5
CRT + ND	3	13.0
TLM, CRT + ND	1	4.3
RT + Cetuximab (Erbitux®)	1	4.3
Length of time since treatment (months)		
0-12	3	
13-24	7	
25-36	6	
37-48	5	
49-60	2	
Carers		
Age	**Median**	**Range**
	66	50-70

Sex	Number	Percentage
Male	1	9.1
Female	10	90.9

Table 7. Participant characteristics

Abbreviations in table: BOT=base of tongue; CRT=chemoradiotherapy; GP=glossopharyngeal; HPV=Human Papillomavirus; IMRT=intensity modulated radiation therapy; MRND=modified radical neck dissection; RT=radiotherapy; TLM= trans-oral laser microsurgery; ND= neck dissection)

When categorised by the English Index of Deprivation (2015), 8 participants (6 patients and 2 carers) resided in areas between the 1st and 5th deciles (higher deprivation) and 16 participants (9 patients and 7 carers) resided in areas between the 7th and 10th deciles (less deprived). This index is a relative measure of deprivation which combines information from seven domain indices (which measure different types or dimensions of deprivation) to produce an overall relative measure of deprivation for a small area. There was no directly comparable measure for deprivation or affluence in the US, so educational level was taken as a measure of socioeconomic status. Seven of eight participants had university or college degrees; four were advanced degrees, two bachelor degrees and one an associate degree. One participant did not provide this information.

Compared with the tenth annual report of the National Head and Neck Cancer Audit [260] for data from 1st November 2013 to 31st October 2014, the proportion of base of tongue (BOT) tumours in this cohort was relatively high. In the audit for England and Wales, tonsil tumours were nearly twice as common representing 49.6% of all OPSC compared with 27.7% for BOT. In this cohort 34.8% of participants had tonsil tumours compared with 56.5% BOT. HPV status was not available for all patients in this cohort or in the audit, because not all patients had testing. Of those that did have testing, 62.5% in this cohort were positive, which is similar to the audit in which over 70% of those tested were HPV positive. The first active treatment for the majority of patients in the audit was non-surgical (55.7%),

this was very similar to this patient cohort in which 56.4% of primary active treatments were non-surgical.

3.5.2 Outcomes identified

The results are presented under titles relating to the themes in the topic guide e.g. 'Diagnosis, priorities and treatment decisions' relates to questions around their diagnosis with cancer, priorities at that point and following and the factors that influenced their treatment decision. The section on burden of presents the outcomes relating to treatment associated morbidity. Activities and participation relates to discussions around normal participation in every-day life. Process issues to themes around the actual delivery of treatment and rehabilitation. Effects on relationships presents the themes arising from discussions around relationships with those close to them. The subheadings relate to the outcomes actually described by patients and carers. In total 136 distinct outcomes were described by patients and carers during the course of the interviews. The outcomes contributed to the comprehensive outcomes list.

3.5.2.1 Diagnosis, priorities and treatment decisions

Discussion around treatment decisions helped to illustrate what patients' priorities were prior to embarking on treatment. At diagnosis, most patients explained that their first thought had been whether they would live or die, as one said *"cancer is cancer and it's frightening" (C2*). This fear suggested that survival was the most important outcome for many, particularly for younger people and those with caring commitments. As one young mother admitted *"I just couldn't afford to fail, so I didn't think I was going to." (C6)*

Several patients described "not hearing anything" after they were told they had cancer, and two were unaware that they would even need radiotherapy after their

diagnostic consultation. Few patients recalled being given treatment options with one saying *"It's a relatively binary choice isn't it- live or die." (C1).* Another patient, who enquired of the clinician what would happen if he did not choose the recommended treatment recalled having been told *"'Well, you die."* This patient explained that he did not hesitate further in going with the course of treatment his clinician had recommended, saying *"That's it, book me in! And have it done and that was it." (C4).* Many patients said they would have agreed to do whatever the medical team had suggested, one even questioning the value of doing any research at all:

"You get all the pamphlets from the hospital and they give you an... a website that you can go on and get, well I, I couldn't, I couldn't see the point of wanting to understand something when in fact you're in the hands of the experts and I just thought well you know, get on with it." (C15)

The majority of patients took this stance; that they were in the hands of the experts and they would go with whichever treatment was recommended. However this was less common in the US where patients tended to have done more of their own 'research' and may have seen other clinicians prior to coming to MDACC. Fears about survival were allayed for several patients because of reassurance of a good prognosis by their treating clinician. However, looking back at these early consultations in the light of their experience of treatment, many felt that the long-term side effects of treatment were underplayed:

"I thought it's going to be severe, but you get through it and then you may have some problems. But I thought they wouldn't last forever, so whether that was my perception, eventually the taste would come back, the saliva would come back, everything would come back... And when they didn't that was the hard bit" (C12)

Others recognised the quality of life issues but rationalised that the adverse effects were of less consequence and worth it for survival:

"The quality of life that I think is important to everybody. And to know that I've got really good quality of life. It hasn't left me, you know, like with one arm missing. It's left me with a few little quirks, but nothing major." (C6)

Several MDACC patients shared the view of C16 that "the likelihood of a cure is just better here than anywhere else". All patients in the UK were treated by their local MDT. None held the impression that treatment would be better elsewhere, although two patients who missed out on a Tomotherapy trial (because cancer waiting times necessitated an earlier start to their treatment) described now wishing that they had waited for this trial, believing they would might have suffered fewer adverse effects.

Several of the US participants were professionals and entrepreneurs, and they placed greater emphasis than the UK patients on the need to return to work.
One patient, who was himself a doctor, was particularly keen to avoid open surgery, which had been offered in another centre and had chosen MDACC because *"I basically wanted the highest cure with the minimum torture." (C16)* Whilst he attributed his desire for a less invasive treatment strategy to the need for a good functional and cosmetic outcome to continue his practice, his wife, who I also interviewed, suggested cosmesis wasn't his primary concern but that the 'less invasive' nature of a non-surgical treatment approach was appealing. He re-iterated several times that he "hated hospitals and doctors" and seemed to find relinquishing control and 'being the patient' difficult. Thus my interpretation was that he had selected MDACC specifically for proton therapy, which he perceived to be the least burdensome treatment option.

Survival

Nearly all patients found the side effects associated with radiotherapy the most troublesome part of their treatment, with the greatest treatment related morbidity and length of recovery. Yet, all patients said they would have the treatment again, given the choice, if it led to their survival. Survival was universally prioritised as the most important outcome to patients and carers.

Survival meant slightly different things to different people, however. Some qualified survival by focussing on certain milestones or living long enough to see an important event such as a child's wedding or seeing grandchildren growing up. Others, especially those with young children talked about survival in more absolute terms:

"cure in the sense that you are 'gonna' be around." (C6)

For some older patients, whilst survival was still their priority, they were more focussed on short term goals and C5 said "to tell you the truth I, I live day to day":

"You're not looking forward to planning things for the next five years or something like that or, or things like that. So err as I say the, the most we, we look forward to is probably four months pre booking of a holiday ((laughs))." (C5)

C23 questioned whether he would go through treatment again were he older, stating *"If I was eighty, I might say no."* For him, quality of life would be more of an issue than survival at this point.

Box one, overleaf, shows some of the other themes around survival that arose.

Box 1. Survival

Trade-offs

"The treatment was more brutal than the disease itself, but I had to have that brutal treatment to stop the disease. So, you know, it's a trade-off isn't it? It's either get really, really ill... And then, or slowly get ill and then die. So you, sort of, trade it." (C6)

Advancing age and changing priorities

"My whole family was like "Ok, Ok, we gotta know, if it came back would you go through with it again?" I said "Yeah. If I was eighty, I might say no, as long as I've got a chance to watch them get older and see my grandkids grow up, yeah, I'll get through it again." (C23)

Survival to a point

"As far as the future, the future goes, um, you know, er, yeah, I, er, I am positive about it, um, and like I say, er, I have got to make sure that I walk [my daughter] up that aisle." (C7)

Survival for others

"I've always been in the erm children's lives and I always want to be because erm I am important to both of them because erm, well we see them, we see them every day really and so yes, I am important and I want to continue to be." (C2)

Fear of recurrence

For many patients and their carers, fear of recurrence was highest in the days to weeks before their follow-up appointments:

"I know he worries every time we drive up to [the hospital], and that, he is worried that it will come back and that he will have to go through the whole thing again. I

think he worried initially for his own mortality I think, but… although he tried, he said that he felt very positive about it, because he was told that the outcome was quite, would be good, he still worried for his, he's still worried for his own life." (CC1)

This anxiety would subside after getting the 'all-clear' at their appointment. One patient who I interviewed the day after his follow up check said:

"I mean the cancer certainly isn't weighing heavily on me and erm it was weighing a little heavily yesterday" (C16)

For this reason many patients were glad when follow-up periods were extended; to them it meant the clinicians were less concerned about the cancer coming back and it meant fewer appointments with less frequent spells of anxiety in the lead up to them. In the UK, patients are followed up for 5 years from the end of treatment and then discharged if they are disease-free. One patient described the follow-up as being *"like a sentence", "a five year thing and I'm two and a half years through it" (C2)*

Some viewed the 5-years as a big landmark - once they reached this they would feel "off the hook" - others admitted that they felt they would always be concerned about their cancer coming back, however the intensity of these concerns seemed to lessen as time went by.

Worries about recurrence kept some patients awake at night, and several commented that any kind of throat symptoms made them anxious that their cancer was back. For many this stemmed from their cancer being so indolent in the first place; they did not know what to look out for and were worried that they would miss it again. Anxiety about recurrence was more prominent in the accounts of carers than patients. There were concerns about recurrence and the need for more

intensive treatment, death, and also concerns, for some, about how they would cope if their partner died:

"I think I tend to probably worry a little bit more because I know CC4P doesn't worry so I thi- probably I worry a bit more about um ((tuts)) like I suppose like everybody um you know, financial security, you know, as you're getting older." (CC4)

Many carers felt that their partners downplayed concerns about recurrence, so whilst fear of recurrence was less apparent in patients' accounts this was perhaps because they were masking their real concerns.

3.5.2.2 The burden of treatment

Treatment side-effects

Few patients had symptoms from their tumour, with several commenting that they "weren't sick until they started treatment". The burden of treatment was substantial for many patients with multiple adverse effects of treatment limiting their ability to live a normal life. Indeed, the nature and severity of the adverse effects of treatment overwhelmed many patients:

"[Radiotherapy] was horrible. It was the hardest thing that I've ever been through. I never had any pain or any kind of physical feeling with the cancer, the treatment felt like it was going to kill me." (C23)

All but two patients in this sample had multi-modality therapy and without exception, these patients described the adverse effects of radiotherapy as the most difficult to deal with, one patient commented:

"The operations, I could cope with them alright, it was just the radiotherapy which knocked me for absolute six." (C7)

At the outset many patients reported having scoffed at the suggestion that they would require a prolonged period of time for recovery, and many assumed they would be able to return to work and usual activities at the end of radiotherapy:

"I can remember the specialist nurse saying, it was, I think it must have been when I was having my PEG fitted, um, you won't be back [at work] by Christmas, you know, it will probably be Easter. And I was thinking EASTER, but this is, like, only September, you know, what's going to be going round till Easter?" (C10)

This seemed to be because few expected the adverse effects to be as severe as they were. Most patients felt that the clinical team underplayed the likelihood and severity of the adverse effects of treatment, and several postulated that clinicians deliberately withheld information from patients, who would not go ahead with treatment had they known how difficult it would be:

"It's very clever what they do, but you don't realise how clever until it's all finished and you look back because they only tell you just as much as you need to know on that particular day." (CC7)

Others, acknowledged that the discussion of 'quality of life' issues did occur at least to some degree, however this simply 'went over their heads':

"Neither of us expected that he wouldn't be able to eat certain things, or, um, he wouldn't be able to taste anything anymore, or he wouldn't be able to-, all his saliva had gone, he wouldn't, none of us expected that. Mr W had talked about different, sort of, treatment, or the type of treatment, and that, and what would be the best, um, outcome for the, you know, the patient's sort of long term health

benefits, or whatever. Er, quality of life, that's right, that's what he said, but we just didn't, that sort of went over our heads, we were just, didn't, didn't even anticipate that there would be anything different really." (CC6)

Carers generally seemed to hold more negative views of radiotherapy than patients, with CC1 saying "*I would take my chances"* rather than have radiotherapy treatment. This stood in contrast to patients, who although they all described the very difficult and traumatic impacts of radiotherapy, not one said that they wouldn't make the same choice to have it again – if it cured them. Coming face to face with the possibility of death seemed to have galvanised their determination to live, irrespective of the adverse effects of treatment.

Impact on eating and drinking

Most prominent in patients' accounts were the adverse effects of treatment on their ability to eat and drink. There were several barriers to eating and drinking. Pain was a problem for some patients following tonsillectomy and/or trans-oral laser resection of their tumour, as this gave rise to a sensation of *"swallowing cut glass"* when trying to eat *(C7),* although this generally only lasted for a couple of weeks after surgery. For most patients, pain related to radiotherapy treatment, was the most significant. This was caused by radiation burns to the mouth, throat and neck, which made chewing and swallowing very difficult and was a disincentive to eating and drinking:

"you start not wanting to, to swallow or to eat, and stuff like that, because you know it's going to hurt." (C6)

Some needed enteral feeding via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube to maintain nutrition and for some, hospitalisation to manage their symptoms. Radiation related ulcers were not only painful, but contributed to nausea:

"The radiotherapy to the neck em… it's horrible it's disgustingly horrible, it knackers up your throat, you get ulcers, ulcers become septic, septic goes into your stomach you throw up feel ill, that's basically it.". (C1)

Nearly all patients had certain foods they avoided either because of taste disturbance, pain, mouth dryness, difficulty swallowing or difficulties chewing related to ill-fitting dentures. Adverse effects on eating and drinking were also associated with chemotherapy, and several patients complained *"The worst thing with the chemo was I was constantly really sick, constantly nauseated." (C17)* although, as noted above, several felt that the radiotherapy had caused their nausea *"There really wasn't a whole lot during that period except pain and nausea. I had quite a bit of nausea, I thought nausea only came with chemo treatment and found out mine started almost immediately with radiation." (C23).*

When considered together, pain, taste disturbance, altered secretions and nausea had a profound and cumulative detrimental effect on the ability of many patients to eat and drink during and in the weeks following radiotherapy treatment, described by one patient as a significant *"disincentive to eating" (C23*), another commented:

"I couldn't eat, I just could not eat, and I didn't feel like eating. Um, I was struggling swallowing, the dryness in the mouth, the tenderness. And obviously just the pain as well, because I had the pain in my shoulder, and I think if you have got like a nagging, nagging pain, you just don't feel like eating all the time." (C7)

For most, eating and drinking gradually became easier following treatment, however there were a number of other difficulties related to eating and drinking in the long-term and all patients had adjusted their diet to a greater or lesser degree to accommodate these changes. Dental extractions were also required for many patients and some struggled with ill-fitting dentures following radiotherapy related

changes or because of mouth dryness. Others had difficulty chewing because of restricted mouth opening and pain in the jaw, and for some a multitude of factors led to ongoing difficulties with eating and drinking:

"Just the whole mouth opening, lack of saliva and not being able to swallow, and not being able to talk while I am eating. And only being able to eat, even when I do eat, it's a teeny plateful of whatever it is. And it's exhausting, eating is exhausting; it makes my jaws ache, um, er, I can only get tiny pieces into my mouth anyway." (C10)

Taste disturbance

Taste disturbance appeared acutely during radiotherapy and for most patients never returned to normal. During, and in the weeks following radiotherapy, food was often described as tasting like 'cardboard' or 'metal' and water or nutritional drinks like 'oil' or 'lard'. Most patients had a heightened sensitivity to spices, saying they could *"taste spice where there isn't even any spice." (C10)* in some cases describing tomato ketchup or bananas as spicy:

"You start off with like this baby mouth on one side, where it's like I couldn't even go near a Korma ((laughs))… spices, or peppers or anything that's got a lot burns. And you have to get used to flavours, and how things taste." (C6)

Many patients were unable to eat their normal diet saying that they *"suffered things they would have enjoyed before" (C1)*. All patients had long-term reduction in the sensation of taste. This seemed partly related to the direct effects of radiotherapy and partly to a reduction in saliva. This was quite disorientating for some patients initially, especially when combined with a generalised sensory disturbance in the mouth.

Weight loss

An inevitable consequence of these difficulties is weight loss, and this was mostly described by patients and carers as a negative experience. Clinicians had emphasised the importance of weight maintenance and for many, the struggle to maintain weight became a significant source of anxiety. They were concerned they would no longer fit their radiation mask and would need to have treatment delayed to be re-fitted. Others were concerned that they were less likely to be cured if they lost more weight; that their ability to 'fight back' would be hindered. Furthermore, despite high calorie intake, many patients were unable to maintain their weight:

"It was really hard to keep the weight on because it was extremely hard to eat. I basically lived on 'Ensure' more than they said they regularly ever see anybody do it, I was drinking six or eight bottles a day and that was all, but, you know I was getting over two thousand calories that way but I was still losing weight hand over fist." (C23)

Anxiety about losing weight was most prominent in the accounts of carers, who were often given the responsibility, by healthcare professionals, of ensuring that their spouse maintained an adequate oral intake. As a result, meal times often became a source of friction for couples:

"It's hard for someone to understand when you haven't taste or when after a couple of weeks of radiation and chemo everything tastes terrible. And the nutritionist is telling my wife 'you've got to make him eat' and she's telling me to eat and I'm saying quite frankly it's like eating out of the bottom of a sardine can, I mean it was awful, everything tasted awful." (C22)

Some patients reported that their carers were unable to understand that they could not just 'force food down'. One patient, when explaining this to his partner

provided an evocative analogy to explain the difficulties of eating during radiotherapy:

"'Tell you what, I'll make myself take a bite of the food and eat it if you will take a bite of a jalapeño, before you eat a bite of food, and we'll both keep eating as long as you want to and as long as you'll take another bite, you know you might get by with that one or first two bites of that jalapeño but when you have to eat a third, or fourth, or fifth jalapeño you're gonna say 'No!' you're gonna stop eating, and that's how it is for me.' When you were nauseated you had no appetite, and it's really hard to eat when you're nauseated and food tastes wrong, and it hurts, it's just like 'Who would eat' in that situation?'" (C23)

Interestingly, a few patients who were overweight before treatment did not mourn this loss as much and enjoyed being slimmer. C1 said he was 'dead chuffed' after trying to lose weight for years unsuccessfully. C16 enjoyed the fact that he could eat what he liked and not put weight on, saying: *"In the old days when I would frequently eat a pound of BBQ potato chips in a day, I'm staying thin now and don't have to work at it at all!" (C16)*

For C, her weight loss was positive in the respect that she had always wanted to lose weight but negative in the sense that she had no control over this and there was a certain sense of loss of identity.

"It's strange, because it, it, you always want to be… I was always big, even from when I was a kid I was big, you know, that was me. And then all of a sudden I am not big anymore." (C6)

Socialising around food

Changes from normal eating and drinking patterns were especially difficult for patients who had previously socialised around food and drink, as this was no longer something they could enjoy as much, if at all:

"[Life] is totally different because I loved eating and I loved drinking wine. Um ((coughs)) and now, even if I do, even if I was to try and eat - which I do try and eat something every night - I can't eat with other people because it's such a difficult thing. And I certainly can't talk when I'm eating. So socially, um, it's just a, you know, it doesn't exist." (C10)

One patient made the point that this was likely to bother him "more than the person who probably eats at home every night." Saying:

"We were fairly social people. Erm… I had a wine collection worth $100,000 so I had a lot of wine and couldn't drink it. So yeah I would say it might have been more… I would say a farmer from Iowa who's pretty much eating at home would find it less difficult. He might find it as difficult to eat things but it wouldn't bother him as much as it bothered me." (C22)

Some patients who had transoral laser microsurgery (TLM) described a sensation of the throat being tighter on the side of the surgical resection meaning that they had to take smaller bites. Combined with their lack of saliva, meals took much longer to eat, meaning they were unable able to finish at the same time as the people they were eating with. Nasal regurgitation was another problem in this patient group as a result of surgical removal of the soft palate. This was socially embarrassing and, for some, meant that they avoided eating in public:

"It's embarrassing when I'm out, if I don't get my breath right the whole, everything, food, everything just… I'll have a tray here and the whole lot'll, everything pours down my nose." (C8)

Eating and drinking for many required significant focus, and was no longer an enjoyable activity, especially when in public.

Mouth dryness

Changes in the consistency of saliva generally started towards the end of radiotherapy treatment with several patients initially complaining of foul tasting, mucinous phlegm which they were unable to swallow.

"I can't emphasise enough the muck that was coming up into my neck and mouth. ((cough)) It was disgusting. It was just all, there wasn't no let up from it." (C8)

The consistency and amount of saliva generally improved, although this didn't return to normal for any of the patients and swallowing remained difficult for many:

"I've not got enough saliva, or I have [[ate]] something that's quite drying, and I have not realised how drying that really is. And then I have gone to swallow it and it's like, no, that's not happening!" (C6)

For many, their diet had become less healthy, the mouth dryness imposed several dietary restrictions:

"I loved salads, and, I mean, I was a healthy eater. Um, I mean, I liked rubbish as well, but I was generally a healthy eater, and I can't eat anything like that now." (C10)

These effects had a significant impact on patients' enjoyment of food, with many 'eating to live'. One patient had significant anxiety around eating, because this continued to be very difficult:

"Eating problems haven't changed, it's still no fun… Oh God, I just don't want to go to the table, I dread it. I dread it. It's just a chore." (C8)

Patients and carers described mouth dryness as having a cascade-type effect - leading to, or contributing to, many other problems:

"It's his dryness of his mouth which affects everything, you know, it affects his sleep and the conversation, as I've said, it's really - They say dryness doesn't do it justice, it's really life-changing for him." (CC7)

Many patients talked at length about the lack of saliva itself and the multiple secondary effects of this. For many this was an acute and long term effect. In addition to the problems associated with eating and drinking, which are well recognised in the medical literature, there were a number of other effects, which are less well documented. These are illustrated in box 2.

Box 2. Mouth dryness

Anxiety about oral hygiene

"[crisps] get in your teeth, and they are all in your mouth, and you get quite, I don't know… but I like to make sure that, you know, like, I have a mouthwash before I go to bed and when I get up. And it's just because ever since the operation, when I get up, I get up and I feel like di-… it feels like somebody's died in my mouth." (C6)

Tiredness when speaking

"I was a deputy head teacher in a primary school; I can't even read a story to my grandsons now ((coughs)). Partly because my mouth gets so dry, and partly just because when I start just speaking without a break, as you are doing when you are reading a story, I am absolutely exhausted by about the fourth page or something."(C10)

Inability to exercise

"I just can't do anything [exercise] because I can't, my mouth gets so dry and I can't take a drink unless I can hold my breath, and you can't hold your breath if you are out of breath." (C10)

Interrupted sleep

"I'm waking up every hour and a half anyway because me mouth just dries up so… I have to take a bottle of water now just I don't know how to put it, it's like a bit of leather all shrivelled up so, I wake up every hour, hour and a half." (C3)

Swallowing

In the short term, radiation related pain and mouth dryness had the greatest impact on ability to swallow. Oropharyngeal resections had very temporary effects, only lasting a couple of weeks, in this patient cohort. In the long-term, swallowing was affected by a number of factors. Radiation caused hardening and stiffness in the muscles in the mouth and tongue leading to difficulties chewing food, forming a food bolus, propulsing to the throat for swallowing, and then difficulty initiating a

swallow. Several patients had radiotherapy related oesophageal fibrosis which meant that the oesophagus was narrowed. It was therefore difficult to get food down. Reduced saliva meant that food was poorly lubricated and more difficult to swallow. One patient had problems with food going 'down the wrong way' into the lungs and causing chest infections. This can be sequelae of both the cancer and the treatment.

Fatigue

Fatigue was a significant problem for many patients during and immediately after radiotherapy. This had implications for those with other caring duties who were unable to care for their children, pets or elderly relatives. For some this meant they were unable to travel to radiotherapy and ended up requiring hospitalisation. This was something that most patients strongly wished to avoid, in many cases because of their own commitments as a carer to others, especially children. Fatigue was another factor that contributed to difficulty with eating and drinking. The level of fatigue was so great for some patients that they would often want to sleep through mealtimes and would have little energy to have a meal, which was already a difficult task.

Some patients described how fatigue persisted into the long-term, with some complaining of a lack of 'Get up and go' or a loss of 'Mojo'. Patients had to reduce their working hours and several continued to have naps during the day or in the early evening, often 'hitting a wall' after only a few hours of activity. This was particularly troublesome for patients who were unable to fill their obligations as a parent or in their place of work. For many it meant that they were unable to return to exercise or evening activities after a day in work.

Tube feeding

The requirement for enteral feeding was seen as 'failure' by many patients. This seemed to stem from the way that it was described as a 'last resort' or something to be done if they 'weren't managing'. Similarly, some patients were concerned that they would never swallow again if they accepted enteral feeding and took great pride in having avoided this. Some described being 'determined to avoid' (C1) enteral feeding, in some instances against medical advice (C6), as the procedure seemed to signal the beginning of a 'loss of control' and a slippery slope towards increasing medicalisation and eventually hospitalisation. For those patients who could not avoid tube feeding, most opted for a PEG, several saying they would feel more socially isolated with a NG tube, because this would be visible to others.

Several patients had technical problems with their PEGs which were a significant source of anxiety as some described feeling that their 'life depended on' their PEG. One patient (C8) found the PEG to be unhygienic, saying that he was concerned that it had an unpleasant smell and that the device would often get caught under the toilet seat. He admitted to being quite a particular person and for him the PEG was a considerable challenge. Others were conscious of the appearance of the scar following PEG removal.

Dental extractions and jaw problems

Some patients required dental extractions prior to starting radiotherapy and several commented that they were keen to avoid this;

"They put the fear of the Lord into me about losing all my teeth and I can never have a crown… but if I ever were to get punched or break my jaw it will not heal without a bone graft so that did make me think that I'm willing to put these things in my mouth every night." (C16)

Many patients were concerned about losing teeth post-operatively and of developing osteoradionecrosis of the jaw.

Shoulder weakness

Only patients who had had neck dissection complained of shoulder dysfunction. Some attributed this to the surgery and others to radiotherapy. This had significant consequences for some patients. One had to change jobs as he was no longer able to undertake the manual nature of his work, a second had to sell his motorbike as he was no longer able to hold himself in the position required to ride. Several patients were no longer able to play sports which they had previously enjoyed, and poignantly one was no longer able to take his children out with their horses or skim stones with them. Pain was also a problem in this group and one patient found it hard to eat because of the 'nagging pain' in his shoulder and another felt that it disrupted his sleep.

Altered appearance

Some patients were concerned about their changing appearance and others' perception of them. For some this related purely to their physical appearance; loss of muscle bulk and looking 'like a skeleton'. For others there was more of a concern about the connotations of being underweight, with one patient concerned that he looked like a 'drug user'. Another was concerned that his radiation dermatitis made him look like a 'leper'. One patient had a severe skin reaction to Erbitux®. He found this particularly challenging because it was outside 'the norm', and not a usual adverse effect of cancer treatment:

"There are a lot of people here with no hair but there aren't a lot of people with open sores all over and you feel, you don't want to go out to eat, you don't want to go to the cafeteria hardly, you just want to get your radiation treatment and come back- because it's ugly." C22

For one patient (C1), the wound from his neck dissection was longer than he had expected and he thought the surgical clips, drains and lines would be alarming for his partner.

Many patients had neck dissections as a part of their treatment and several men complained of having a 'scrawny' neck afterwards, meaning they had difficulty fitting shirts. A female patient grew her hair long and wore it down to hide her neck dissection scar, because this often prompted questions from people who did not know about her cancer and she preferred not talking about it.

"... if I was to meet a new person I have my hair down, I don't have my hair up. I don't talk about the cancer to people that I've just met, or I don't like talking about it to them. And the people around me, we don't talk about it unless something relevant comes up, and then they might say like, this, that and the other. So I think it's just having that conversation, because it's just, you know, when you are trying to get to know somebody, and somebody goes oh, well thing, and what's the scar from? Oh, I had cancer? Oh really, well… Yeah, people really do get awkward about the subject." (C6)

She did, however, speak of being proud of her scar as this reminded her of what she had survived.

"I feel like I have been incredibly lucky. I feel quite, I am proud of my scar, um, because it proves that I have been through something and, you know, I am, I am stronger for that." (C6)

Others said they did not want a scar because they felt this would be a constant reminder of an awful time. Others felt less likely to have chosen a treatment option with a risk of a scar.

"I often think if they had said to me do you want surgery or do you want the treatment, I would have probably chosen the treatment thinking, well I don't want a big scar on my neck." (C10)

Some patients described their smile as 'wonky' following marginal mandibular nerve palsy. In some cases this resulted in drooling and cracked skin at the corners of the mouth as a troublesome consequence. One patient, following injury to the spinal accessory nerve and the marginal mandibular nerve following neck dissection, described himself as 'disabled'.

"... that's been hard to deal with because the way it's left me mouth, it's left me like disabled sort of thing because I can't raise this arm anymore as high as this one, em, the shape of me body is like this, me body's like lop-sided. I feel like my face is lop-sided this side's stopping em... I started having different sensations, even now around me lips" (C3)

Several patients had persisting skin changes as a result of their radiotherapy including redness, thread veins, dry lips and thinner hair. Lymphoedema was an issue for some patients, particularly one woman who wore a scarf to conceal it. Interestingly, despite these concerns, she still did not do the recommended exercises.

Speech and voice

This was another factor that was more important for some patients than others. For some a change to their voice was something that they found funny or a mere irritant, for others this represented a 'change of identity' (C12) and was one of their 'greatest concerns' (C12). One patient was unable to return to work as a teacher and engage socially as a Soprano singer because of the effects on her voice:

"*I can't sing, obviously, my voice is so deep now, um, I can't, and I used to sing a lot." (C10)*

She was also unable to read stories to her grandchildren because her mouth would become too dry.

"Um, so when they are singing things that they have learned at school and I want to sing with them, I can't; things like that really frustrate me. Um, reading to them, I would love to be able to do that." (C10)

Some patients described their voice as 'clacky' (C9) because of their mouth dryness, and as noted in box 1 above, several said that extended conversation was 'tiring', requiring regular drinks to be able to maintain conversation (C6). Another was unable to project her voice and had a tendency to withdraw from conversation in social settings because she struggled to make herself heard (C10).

Social life was very important to C3, and he noted that his partner had commented how lucky he was that he could still enjoy karaoke, one of his favourite hobbies:

"We go to town every Sunday and like she's going…. Sorry… (becomes tearful) … eh she knows how much I love the karaoke so she was like god help you you can still sing you know what I mean so that was like… and I wasn't myself with the social life." (C3)

He became tearful discussing this, and described his social life as '*the main part of me life' (C3)*. For him any withdrawal from social life would have been *'a killer' (C3).*

Psychological well-being

Low mood and depression were common during and immediately following treatment. For many patients their lives had changed completely, and they were no longer able to do the things they would have done before. For example, the loss of vocation was difficult for C17 who had worked and been a volunteer before starting treatment:

"Part of that depression was, I would get up and "What am I going to do today?", I don't have a job, not healthy enough to go do this, what do I do with myself? I can't just sit every day, you know I don't like to watch TV and I don't like to become mindless." (C17)

C13 and his partner, who had a joint interview, felt that he had managed his mood well during treatment, but that his depression arose when he had difficulty returning to normal activities:

"I did sense that it was a little bit of depression there as well. And I put that down to um not being the person I was before that, before everything that's happened." (C13)

Another patient attributed his depression to difficulties with eating and drinking and a frustration at his circumstances:

"I was depressed because I couldn't eat, and basically at my age, I own a company, I've got plenty of money to do things I want to do and here I was, I'd been stuck in either a hospital room or a house for eighteen months, so I was rather depressed." (C22)

C10's treatment had a profound effect on her life:

"It just seems like everything, that everything has been taken away; um, everything I enjoyed has been taken away, basically." (C10)

C23's wife was particularly worried that he would never return to being the person he had been before:

"At some point down the line I was watching a television show and I laughed, and it stopped her in her tracks because she hadn't heard me laugh in months, and she realized how much she had missed it, it practically made her cry, she realized that she really, really missed that, and it was one of those indicators that I wasn't the same person and that scared her to death, that I was never gonna get back to being the same person." (C23)

Two carers described their partners as being depressed during treatment; although the patients themselves had not suggested this during their interviews.

Cognitive decline

Cognitive decline was a problem for several patients after treatment. Memory impairment and poor concentration were particular issues, and several patients had problems finding the words for what they wanted to say. This was of more concern to those still in the work place, two of whom felt their work performance had been affected:

"I have organizational skills err problems now, where I used to be a lot more organized, not that I was really organized but I'm really disorganized now when I start trying to put stuff together and the logic's not always… I'm having issues about trying, how to prioritize and what order it needs to be done, I'm also a bit more forgetful." (C20)

One patient found this a particularly difficult and frightening side-effect of treatment to deal with:

"I'm driving the familiar route and all of a sudden, stuff won't look right to me and it's a little unnerving I'm like "You're in the right place, you're in the right place you don't… I think it's been very [voice breaks] frightening [becomes tearful] and very depressing." (C17)

It also affected her desire to socialise because she had difficulty remembering names:

"What really drives me crazy is people I have known for years, I grew up in this area and we, the girls that I went to High School with - I mean we graduated 52 years ago – we get to lunch together four times a year and I've lost their names. And I look at their faces and I know them and now I don't know their names. It's very frustrating" (C17)

No patients were aware of this possible side effect prior to embarking on treatment and this had very different implications for people, depending on the degree of disability and what was required of them in their day to day lives. One patient felt that her cognitive dysfunction had improved in the time since treatment.

Personality changes

Several patients noticed personality changes after treatment. Some said that they were more emotional, and more likely to cry; some felt their emotions were more 'up and down' and that they were more irritable and quick to anger. One patient admitted that he now refused to queue because he did not have the patience for this.

Dependence on medication

Some patients described having developed a dependence on opiates during treatment, but for a much greater number the fear of dependence meant they used them with caution. Others were concerned about their ability to make decisions on opiates and the impact this would have on their home life or work. Many patients commented that they didn't like taking medication and so avoided this as much as possible – to their detriment at times.

Fluctuating vision

Several patients complained of fluctuating vision during and following radiotherapy requiring several different glasses prescriptions. This was a significant financial burden for some patients. One patient felt even more isolated during radiotherapy because of her visual problems as she was unable to read or watch television.

Hearing loss

Some patients had cisplatin-related ototoxicity and others Eustachian tube dysfunction and glue ear resulting in hearing loss.

Sensitivity to the cold

Several patients complained that they were always cold during radiotherapy requiring multiple layers of clothing. Others noticed that their ear and the area around their neck dissection wound was more sensitive to the cold.

3.5.2.3 Activities and participation

Social isolation

Many patients became socially isolated during treatment because they simply felt so unwell. Many explained that they would sleep much of the day, or be sleepy from opioid analgesics required to manage the pain from their radiotherapy burns:

"When you go through treatment you're really, really sick you get so limited and your world starts closing down and then as you start getting a little better you're real isolated." (C17)

Many deliberately avoided company, or felt that their friends were far less supportive than they would have expected:

"You have what you consider good friends, and you sort of have acquaintances, and it's rather surprising when you're going through the treatment and the people that actually call and enquire and those that don't, and you have the people that you consider your close friends and they may not have called at all in six months. So did it affect some of those relationships? Yes. My cancer did, because you can't help but feel a little twinge of bitterness towards that person." (C22)

Others wished to socialise but found re-integrating to normal society difficult, after quite prolonged periods of social isolation:

"I'd forgotten how to dance 'cause I hadn't been anywhere to dance for years. Remember I've been locked away now for four odd years and it, it upset me... It made me feel my age… I wanted to be with them and I couldn't." (C10)

Lighter duties

Several patients were re-assigned by their employers to lighter duties because they were no longer physically able to do the work required of them following treatment; one because of shoulder weakness and the other two because of fatigue and loss of physical strength. Another patient had to give up her voluntary work at a dog shelter because she was too fatigued to undertake the manual work required. Patients in office jobs did fewer hours than they had done previously and one

patient had been unable to return to work altogether because of difficulties with speaking and projecting her voice.

All patients had to withdraw to a greater or lesser degree from the workplace and hobbies and social activities. C17, because of her fatigue was no longer able to volunteer as she had done previously and felt that she lacked vocation:

"I'm still searching for what I find will make me feel of value... I have to figure out some way to serve because I've always done that. And I haven't found the right place for that yet, or how I'm going to do it, and I think I have to go further down the road and get healthier, where I'm feeling better." (C17)

For many there were significant financial repercussions of their cancer. One patient in the UK lost her carers allowance as she was no longer able to care for her mother and was not entitled to other benefits or income support.

Travel

Travel and outings were difficult for patients who had problems with eating and drinking. Several patients preferred to eat at home where they could prepare something they knew they would be able to eat. Others were less inclined to travel because they would have to explain their problems over and over again to restaurant staff. Some patients travelled abroad whilst still PEG-feeding, this was a significant logistical challenge. Therefore patients' social worlds had got smaller:

"I was never a really outgoing person, um, but I was fine around other people; whereas now I'm just, you know, I really love to come home kind of thing. Um, so that's, I mean, that's made things quite difficult really." (C10)

For C10, this was partly because she had become more introverted since her cancer treatment but was also related to difficulties with eating and drinking.

Exercise

Few patients were able to exercise as they had previously, largely due to fatigue, loss of physical strength and mouth dryness. One patient who had enjoyed circuit training, was worried about returning and being unable to do as many repetitions of exercises as he had done previously. He was worried about what other people would think of him and he was worried about letting himself down; not being able to do as many repetitions of an exercise would show, in an objective way, that he was less able than before. As in the section on mouth dryness- for several patients this is what held them back from exercising.

3.5.2.4 Process issues

Masks

Moulded masks are used to keep patients in position during radiotherapy so that the treatment dose goes to the correct place. The process of making the mask was traumatic for some patients:

"When you are getting masks fitted and everything that was a horrendous experience, um, and being fastened down to the table, I mean, that is just, oh, horrendous!" (C10)

Being 'pinned' down for treatment everyday was extremely distressing for some patients. This became more of a problem as treatment progressed, and patients were dealing with nausea and thickened secretions which, normally, they would spit out. For many there was significant concern about dealing with these secretions or vomiting when flat, and aspirating and asphyxiating.

"I was terrified of being, lying flat on my back with a mask while feeling this terrible nausea and having just been vomiting that morning I was fearful of aspiration and could I get out of that mask quickly enough." (C19)

For some, the mask was a symbol of what they had endured, and one patient had kept hers:

"I think it's because being strapped to that table with that thing, um, and being left while they walk out the room, I think I took all my anger at it out on that, and now I just don't want to ,- ((laughs)) I think, um, that's just a reminder. I just don't want, um, before I took it for granted, and I took life for granted, now I don't want to ever forget what a gift I have been given." (C6)

Others never wanted to see their masks again as they had such troubling memories of their radiotherapy sessions, and did not want a reminder. Many patients talked about not wanting 'reminders of treatment' or 'reminders of their cancer', and this was a reason many gave for preferring non-surgical treatments over surgical treatments, because a scar would be a reminder.

Keeping up with the schedule

To maintain swallowing function at a good level after treatment, MDACC patients are encourage to undertake intensive swallowing therapy, MDACC patients may also be given fluoride trays and exercises for trismus and lymphoedema. The schedule of activities was really quite overwhelming for some patients, particularly in the midst of their treatment, with one admitting that she contemplated suicide as she became so overwhelmed and depressed by 'having to do so much' and the burden of expectations upon her:

"I had some low spells of occasional suicidal thoughts because you have to do so much, you have to do the swallowing exercises, I had to do fluoride my teeth, do

this, do that and all that stuff I was good, and I thought [whispers] is it ever going to stop, and little by little it drops off and as it drops off it helps, but I've had sometimes where I've had several days I couldn't do anything, just so fatigued, and I felt like I'm letting my husband down." (C17)

C16 "hated" doing his exercises and accepted that he was more likely to need enteral feeding further down the line if he failed to do them. Even though he was self-conscious of his lymphoedema he also refused to do these exercises.

"I'm supposed to be doing two kinds of exercises, for cosmetic for my lymphedema of the neck and for swallowing exercises and I try to do those at a little bit but it's eh I just it seems like a half hour of misery but if I wind up in fifteen years with a gastrostomy I won't like it but I won't complain. But I'm just not doing the exercises I just don't like 'em and I don't want to do 'em!" (C16)

It seemed liked these were a reminder of his cancer, or treatment, or in fact time as a patient. As a doctor himself, I think he found it very hard adjusting to this role.
Another patient had been advised by a family member treated for head and neck cancer, of the importance of doing swallowing exercises, he was therefore fastidious about doing these but still found it challenging:

"I found it remarkably difficult to do all of the things that you needed to do and wondered how anyone was able to keep a job and do all what they were supposed to do in terms of timing of when you take medications, timing of when you ate and made sure you had plenty to drink, trying to get in some type of exercise, I found it remarkably more complicated." (C23)

In contrast, patients in the UK had a less intensive schedule of rehabilitation, and in fact some felt that they did not receive enough support, particularly with regard to physiotherapy for shoulder weakness following surgery to the neck:

"I think if I was made to have it [physiotherapy] done, my shoulder would be a lot better now." (C6)

Travelling for treatment

For many patients in the UK, the daily travel to and from radiotherapy sessions was a significant burden, and became more of a challenge later in treatment when they were more symptomatic. Patients travelling greater distances were more likely to be hospitalised for management of their symptoms, as the travel was too burdensome.

In all cases, however, patients were willing to travel for what they perceived to be the best treatment. In the US some patients had literally travelled from the other side of the country, one choosing MDACC because *"the likelihood of a cure is just better here than anywhere else." (C16)*. A surgical approach had been suggested for this patient at a different, but still prominent, cancer centre closer to his home, however this patient was keen to avoid cosmetic or functional impairment which he saw as being "career-ending". He chose MDACC specifically for proton therapy, which at this point was not common practice for head and neck cancer treatment.

End of radiotherapy

On completion of radiotherapy at MDACC, there is a tradition of 'ringing out', where a large gong is banged to symbolize the end of treatment and "the restoration of balance, harmony and life energy." For most patients, the real challenges of radiotherapy continued long 'after the gong', both in the US and the UK. Indeed, they described the weeks *after* radiotherapy as the most challenging; their pain and secretions often worsened but they no longer had the daily interaction with clinical staff for support.

"He had that security blanket, that safety net of visiting [the hospital] every day and then that suddenly stopped and I think he had no-one to turn to, no one to talk to and to actually say 'Is this normal, that I'm still losing my hair, that ulcers are still erupting?' erm and we did not know who to go to to ask." (CC1)

For many the continuation of symptoms beyond the end of radiotherapy was unexpected and raised questions in some patients' minds about the effectiveness of treatment; ongoing throat symptoms for some made them concerned about recurrence. Some patients felt their expectations had been very poorly managed by the clinical team which led to much unnecessary anxiety, and anger in some cases.

3.5.2.5 Effect on relationships

The strains of the cancer diagnosis and treatment seemed to either 'make or break' the patients' relationship with their partner. Most patients in this sample felt that the experience had strengthened their relationship, however they acknowledged the challenges:

"My wife and I might slightly be closer now, because of the way that, you know, she stuck in there and said "Thick and thin I'm here" and you know we had some arguments but I think at the end of it we're a little closer probably. I think it could have gone the other way very easily." (C22)

One patient's husband left her when she told him her diagnosis and another patient left his wife just after starting radiotherapy. C1 admitted that the cancer diagnosis *"really does screw up your relationships"* and his partner said:

"I hate his cancer and I hate him for having cancer, but that is my issue… I have just embarked on counselling because I feel unable to move on from that, and I don't want to hate [him]." (CC1)

She struggled to cope with the changing roles within their relationship:

"I am not a very good nurse, I am not a patient nurse, erm and I found that quite difficult, I did find it very difficult to care for him because he is supposed to be my strong rock and he wasn't. He was reduced on occasions to quite a, a little boy and I found that quite difficult to deal with… I was, for a long, long time I wasn't his wife any more, I was his carer, his nurse his whatever and that is horrible… I found it impossible to be both." (CC1)

Many patients stayed at home in the months following treatment, and this time 'in each other's pockets' was difficult for some couples:

"There was a lot of adjustment. Not just with doing the cancer or taking care of the cancer issue but all of a sudden I'm back in the house, you know so we're about to get through those adjustments which have been just about as painful as the treatment itself." (C20)

Several patients and carers commented however that treatment would be very difficult, if not impossible, without a carer:

"You don't tend to look after yourself as much; I don't think men do anyway, and living, living alone, and having all of that, I just don't know how they, I don't know how they would, um, how you would physically cope." (CC6)

Many couples said they were less sexually intimate, either because of fatigue, dry mouth or difficulty mouth opening. A HPV-negative patient worried his partner wouldn't want to kiss him he case she 'caught' cancer from him:

"I went through a stage where I thought she didn't kiss me in case she caught it… that used to play on me head, that was just me I think cos you do start getting all weird feelings that people are looking at you." (C3)

Others had specific concerns about HPV, which are discussed in the next section.

3.5.2.6 Concerns about HPV

There were 10 patients in this sample with known HPV-positive disease, however HPV status was not available for all patients as some had been diagnosed before routine testing for HPV. Two patients referred to the stigma surrounding HPV as a sexually transmitted disease which raised concerns around other people's perceptions of them. One patient (C19), (who was one of two patients who coincidentally had been involved with a head and neck cancer support group), reported having encountered several women with HPV-positive OPSCC who had tremendous concerns about being perceived as promiscuous because they had a cancer related to a 'sexually-transmitted disease'. Many of these concerns arose from the heightened publicity around HPV, oral sex and OPSCC in the media at the time as a result of comments of the actor, Michael Douglas, on the issue.

"And so on the headlines did, what's her name, the Welsh lady… Catherine Zeta-'Did Catherine Zeta-Jones cause Michael Douglas' cancer?" Well you know for a relatively unsophisticated population, particularly of young women with tumors, they're suddenly thinking, 'Oh, did my boyfriend in High School cause me to have Oral Cancer?' and it's, it's a shame it's unfair, but it is there, it's out there, it's very real."(C19)

This patient also described quite astutely the considerable social problems that would likely arise for an increasingly younger patient population with head and neck cancer given the prolonged effects on home and work life:

"As the age scale has decreased for head and neck cancer, I think you're going to address social issues in young families that really haven't had to be dealt with previously, you know this used to be a disease of old smokers, and you know we've got forty year old healthy nurses who have nasopharyngeal cancer and two little kids at home who expect mom to do what mom has always done and mom can't do it for about a year." (C19)

As clinicians we have a tendency to 'reassure' patients that their cancer is HPV-positive because of the prognostic benefits this confers. Whilst some patients were reassured of the positive prognosis, C1 was quite frustrated that this position was taken by clinicians, saying:

"It's a serious thing so there needs to be more done with the doctors instead of "it's dead common, everybody's got it so don't worry about it" which is sort of the message that comes out and almost what you've just said." (C1)

He described a 'stigma' around having a cancer related to a sexually transmitted disease, and was particularly struck whilst watching the television show 'Girls' in which a character had suggested that she could no longer have sex because she had HPV, saying:

"It gets you thinking about whether you should be having oral sex or not again and that kind of thing whereas whilst the answer might be 'No' eh sorry 'Yes' it's not an issue, it's still something in there" (C1)

He had concerns about passing on HPV "Yeah and you know Hello actually I could give you HPV just by shaking hands" and about his son's risk of developing HPV-related cancers and whether he should be vaccinated. His perception of the

'infectious' nature of his cancer meant that his concerns spread beyond his own health, to that of his family and he felt that it was a great burden.

He was also anxious about recurrence of his cancer in the remaining tonsil, and was worried that this hadn't been removed:

"My logic is if it's coming back, that second tonsil is the target… That's how I've rationalised it in my head err if it's coming so it's HPV-16 so HPV's going to hit a man it's going to hit him in the throat. It's going to hit me in the throat, it's going to hit me tonsil." (C1)

He was concerned that there had been no treatment for the HPV infection and that he would still be carrying this and therefore at greater risk of developing a second cancer, in the remaining tonsil.

Another patient intended to have his grandchildren vaccinated against HPV and although he wasn't particularly concerned about the possible link between sexual activity and HPV, he said this was a particular concern for his wife.

Two patients, despite knowing that their cancers were HPV-positive rationalised that their cancer was more likely due to mobile phones (C13) or industrial exposure to carcinogens (C15) despite the latter also drinking alcohol to excess.

Another patient was initially told that he was very likely to be HPV positive. It later transpired that his cancer was not HPV positive and his 5-year survival probability dropped from around 90% to around 40%. This, understandably, caused significant anxiety with regard to the care of his children and the court hearing regarding their custody. Whilst he secured custody of his children, his initial concerns were that the poorer prognosis would be detrimental to his case.

3.5.2.7 How cancer changed peoples' outlook on life

Many patients described a desire to make their lives better following cancer. To do things they had been putting off doing or to value what they had and those around them more. One patient talked about the *'Gift of Cancer'*. He had read about this and felt very strongly that this applied to him:

"As I reached the point where I recognized that I was going to recover and that things were going to be okay again and I was going to do the things I liked to do again, it became a celebration of life, I mean it… really was a gift [becomes tearful], where you get up each morning and you say 'I have another day.' And I wish I could have gone through my whole life that way…" (C22)

Several patients commented that they were less ambitious at work following their cancer. For example, C6, she had come to the realisation that her children did not need more money, just her time, and spoke of how this had changed her focus in life:

"Beforehand I was very, um, in work itself I was on the fast track. I was going to be, like, um, a managers' manager, and then this that and the other. There was a, a definite five year plan in 'thingy'. As soon as I got back there it was a case of, no this is a job that I go in, in the morning, do it to the best of my ability, enjoy the people around me, have a laugh and I come home. This is where my focus needs to be... I've realised, well the kids don't really care whether I can afford this, that and the other, they just want me here." (C6)

C13 felt his cancer had made him more relaxed, and that work was less of a priority:

"I think how life was before was quite pressurised, err with regards to the work side of things, that was the first thing which it seemed... well it's... the work side has certainly changed. There's no doubt about that… you take... you bring your work home as well, and you take your work on holiday as well, don't you. And err that just doesn't happen now." (C13)

Several patients talked about spending their money more freely afterwards; the cancer had been a 'Wake-up call' that they would not be here forever. Others felt they had 'gained more than they had lost' and that their cancer had made them prioritise themselves more:

"*It's quite bizarre, but I think I have learnt more from it than I have lost. If that makes any sense… I think it brought it all into focus that you haven't got as much time as you think. So I started, after I was getting better, started putting myself as a priority, where before I, I don't think I did. I don't think anything scares me now, where before I could be quite timid about things, now I am not… I get out and I meet people, and I do things a lot of the time that I wouldn't have done before*." (C6)

Some patients however, whilst hoping that life would change, slipped back into their usual routines, as described by this carer:

"*I think he wanted to come out of this as a stronger person, with erm… a second bite at the… cherry and I think he, he was going to pro-actively improve his life, health-wise, exercise-wise, take life by the balls and give it a shake, but that's not happened because routine and everyday life just takes over*." CC1

Several patients and carers referred to life *"just going back to normal".* For some this is exactly what they wanted, however others felt that the cancer should have

changed their lives, to make them appreciate everything more and take more advantage of opportunities.

3.5.2.8 Which outcomes are the most important?

Towards the end of each interview I summarised the outcomes discussed by each participant and asked them to rank the outcomes in order of importance. This was to ensure that important outcomes weren't missing, and to assess the way in which they presented their accounts related to their actual outcome priorities.

Survival was the most important outcome to all patients, irrespective of age, gender or HPV status. Interestingly, whilst many patients discussed survival only fleetingly, this was the most important outcome of all, suggesting that the length of time spent talking about something does not necessarily reflect its importance. The challenges encountered with eating and drinking were most concerning to patients, with mouth dryness universally described as the most troublesome persistent adverse effect of treatment. Difficulty swallowing, taste disturbance and fatigue were also particularly prominent complaints, and these could all be linked to mouth dryness, which has many broad ranging effects.

In some cases, I discussed the clinical trials context and the concept of equipoise, asking "If we were testing a new treatment for your cancer, which outcomes would help you choose between treatments?" I would then give examples of some of the outcomes they had mentioned and ask them about survival at this point if they hadn't mentioned it. Some patients had difficulty understanding the concept of clinical trials and I had to abandon this line of questioning. Patients and carers often said that the acute adverse effects of treatment were important and should be measured, however ultimately the long-term effects, were most likely to influence treatment preferences. Several patients said that they would tolerate 'short-term

pain for long-term gain'. For some however, the 'long-term gain' was difficult to see when they were living a very different life due to functional impairment(s). .

3.5.2.9 Personality and coping

The response to treatment varied between patients, however their subjective assessment of their circumstances played a substantial role in how patients negotiated their treatment and recovery. When talking about their treatment some patients complained bitterly of swallowing difficulties, yet managed without tube feeding. Others gave the impression they had a very easy time of treatment but on further questioning, or interview with their carer, it transpired they needed enteral feeding after starting treatment because they were struggling to eat and drink. For some patients it seemed important to maintain a front of stoicism, although it also seemed that some were less inclined to discuss the difficult memories of treatment. These nuances can make the interpretation of qualitative interviews difficult, which is why interview transcripts must be triangulated with field notes.

3.5.2.10 Multiple, additive adverse effects

Multiple adverse effects may have an additive detrimental impact upon functioning and quality of life. The most important outcomes, from which many other problems seemed to arise were mouth dryness, dysphagia and fatigue.

3.5.2.11 Beliefs about how age influenced outcomes of importance

Some older patients thought certain adverse effects of treatment possibly bothered them less than someone younger. C5 felt less anxious about many of his side effects because he knew, due to his advanced age, that these would be relatively short lived and affect his life less than someone younger:

"I would have been more concerned about, about the effects that it err has or would, would have had [if he were younger]" (C5)

Another older patient, felt that his loss of libido was less of an issue than it would have been for someone younger:

"The Cisplatin pretty well wipes out your, your gonadal functions so your libido drops to zero, err testosterone never really returns to a normal level, but then I'm in my seventh decade of life so I, it's not something that's especially important to me but I erm for younger people it's very important and I know that, I know several who found adapting to that was difficult." C19

3.5.3 Patient feedback on the process

Several patients said that they enjoyed the interviews, and for many I think that they were quite cathartic. A carer, reflecting with her partner after his interview said:

"It's almost like you coming along and talking to us has now, well actually yeah it has improved and we've not noticed because for a long time there, seemed to be no improvement in his lifestyle in his well-being erm and it's been so gradual that we have not noticed that." (CC1)

3.6 Discussion

This is the first qualitative study to explore patient and carer outcome priorities for a COS in OPSCC. This study has identified outcomes of importance and allowed me to explore why outcomes are important to different people and how the adverse effects of treatment affect people in their day to day lives. As well as providing patient centred outcomes to be added to the comprehensive outcomes list for the

Delphi, this qualitative study has highlighted the complexity of dysfunction that occurs in those treated for OPSCC pointing towards areas for future research. A reflection on my role in the data collection and interpretation, the key findings, and my analysis of the strengths and limitations of this part of the study are presented below.

3.6.1 Researcher characteristics and reflexivity

Qualitative research will inevitably be influenced by the researcher and one must carefully consider how their own knowledge, biases and the way in which they are perceived will influence the participants' accounts [261]. Upon deciding to use qualitative methods, it was initially thought that a non-clinical researcher would be the most appropriate person to conduct the interviews with patients as they would be less familiar with the clinical condition, treatment practices and free from professional relationships with treating clinicians which may portray them as an 'insider' in the patients' eyes [262]. On further discussion, however, it became clear that a knowledge of the condition may be of benefit in order to understand and interpret patients' accounts of their experiences. In interviews, outcomes of importance could be implied rather than stated and clinical knowledge might help to probe and further elaborate these. This proved to be the case in this study. When independently coding the first interviews, I was able to identify more outcomes and understand their context compared with BY, a non-clinician. I was also able to understand the relationships between different outcomes i.e. that mouth dryness would have implications for oral hygiene and health or that this could impair swallowing in the short and long-term.

Having been introduced to the patients in a clinical environment, by a member of their clinical team, and as a clinician myself, a possible challenge would be to ensure that consent was provided autonomously, and that the patient felt truly free to refuse consent. We therefore invited patients to participate in the clinical setting

but arranged to discuss further on the phone, outside the clinical environment, once they had had opportunity to consider their involvement in the study in their own time and space.

I am a surgical trainee in Otorhinolaryngology-Head and Neck surgery and as noted above have a knowledge of the clinical condition, treatments, multi-disciplinary team (MDT) decision making processes and of clinical trials in OPSCC. My PhD supervisor was also a clinician, and familiar to some of the patients I was interviewing. I introduced myself as a researcher and doctor, whilst being careful to make clear that I was in no way affiliated with the patients' clinical team, and that my primary role was that of a researcher at the University of Liverpool. In order to avoid patients perceiving me as a figure of authority, I described them as the expert and acknowledged that they had been through an experience that I wished to know more about. This was emphasised prior to the interviews, in my discussions with patients when making arrangements, and on the day of the interview.

When patients made statements about clinical matters that were factually inaccurate I did not correct these. When clinical questions arose, I usually made sure to answer these at the end, rather than during the interviews in order to avoid imposing my own concepts on the patient. I was especially keen to avoid answering clinical questions prior to and during the interview to avoid swaying the 'balance of power' in which having shared knowledge, I may have been seen as the 'expert'.

There was some concern that patients may have seen me as an 'insider' or part of the clinical team and that they might have modified their accounts to avoid causing offence. Patients are often very loyal to their treating clinician and therefore may have been keen to present an account of events that could not be perceived to be

critical of them. I was therefore very clear that data would be pseudonymised prior to being shared with anyone in the clinical team.

Some patients seemed to see the interview as an opportunity to complain about the care they had received and some expressed a desire that the interview would improve the care that patients receive in the future, through the feeding back of these complaints to particular clinicians. I was in no way defensive of particular clinicians or practices. I felt it was completely appropriate to let patients have this opportunity to 'vent' and show that I was on their 'side'. Many described the interview as cathartic; they had often felt their concerns to have fallen on deaf ears and one patient said it was nice for a clinician to 'have the time' to listen as they often felt clinical encounters were rushed. As a clinician, I am acutely aware of the time pressures we are under and it was actually very cathartic for *me* to have the time to explore many of these issues. I feel this openness on behalf of the patients confirmed that they did not see me as an 'insider'.

My clinical experience of course influenced the development of the topic guide. From my own practice and knowledge of the literature, I know that functional and patient-reported outcomes (PRO) are important to patients but less consistently measured in clinical trials in OPSCC. I was therefore keen to establish how these ranked alongside more objective outcomes such as survival or disease control; which are more commonly measured. I also know that radiotherapy regimens are very difficult for patients to tolerate, and that perhaps caused me to dwell on PROs rather than probing more into the more objective outcomes.

As a clinician I am also familiar with the concepts of outcomes in clinical trials, however, it soon became apparent from working with COMET's patient and public involvement co-ordinator that these concepts are actually not easy to grasp. Again to position the patient as the 'expert' and myself as the 'student' and in order to avoid imposing assumptions on the interviews, or confuse or intimidate the

patients, the topic guide was designed initially to avoid direct questioning about outcomes in trials but rather to explore the broader effects of a cancer diagnosis and treatment, and to try and identify outcomes from these concepts. The interview process also helped me to develop a familiarity with patients' terms of reference and the language they use to describe events, symptoms and outcomes.

I undertook training in qualitative interviewing and analysis prior to developing the topic guide and undertaking the interviews. BY, an experienced qualitative research supervisor helped me to develop the topic guide and reviewed my initial interviews to ensure that I was using an appropriate interviewing style and language. In my analysis of the data, I found myself, at times, adopting a more deductive approach. Through discussions with BY I managed to identify these areas and look at the data in a more interpretive way.

I am Irish, and my accent, expressions and pace of speech had to be adjusted for people to understand me at times. I had to be very self-aware throughout the interviews to ensure that the interviewees understood my meaning and were answering the question I thought I had asked. Commonality of cultural background was particularly useful in building rapport with some of the patients with Irish connections, both in Liverpool and the US.

3.6.2 Key findings

This qualitative study identified 136 distinct outcomes of treatment to be included in the comprehensive outcomes list. These related to survival, cure, the acute and late treatment related morbidities associated with surgery and radiotherapy and the wider effects that these have on a person's ability to return to life as before treatment. The outcomes prioritised by patients and carers across all interviews were fairly consistent. This suggests that we have identified outcomes of key importance to patients and carers in this cohort but also those likely to be important

to a wider cohort of OPSCC patients and carers. No specific differences were observed in the outcomes prioritised by patients and carers in the UK and US, rather, individual values, interests and employment seemed to have the greatest impact upon how outcomes were prioritised and the adverse effects of treatment negotiated.

Outcomes relating to function and quality of life predominated the discussions, however survival was universally prioritised as the most important outcome when asked to 'rank' outcomes in order of importance. Interestingly, many patients said little about survival or mentioned it only in passing until directly questioned. This may be because death is difficult to talk about, or that my line of questioning did not lead patients to mention it. It may seem so obvious to patients that this is a prime concern that they did not feel the need to mention it explicitly. In this instance, the length of time spent talking about a subject did not necessarily correlate with its value to patients. Survival was the most important outcome to patients, and carers, irrespective of age, gender or HPV status. This was a priority at diagnosis and on completion of treatment. The adverse effects of radical multi-modality therapy did not change this stance. Although there are no studies looking at OPSCC specifically, this supports other research into SCCHN patient priorities [46, 263-266]. Only in studies of laryngeal preservation, are a minority subgroup of patients willing to compromise survival for function [267]. Patient characteristics influenced the strength of feeling about the importance of certain outcomes. Survival was more emphatically prioritised by younger patients, especially those with children and older participants with caring responsibilities for grandchildren. They tended to have a 'survival at all costs' approach to treatment decisions. Evidence from SCCHN studies shows that the majority of patients are willing to tolerate a high level of treatment toxicity to maximise life expectancy [46, 268, 269]. On the other hand, older patients without such responsibilities, were more inclined to question the degree to which they would accept a reduction in HR-QOL in the interests of survival. No patients stated that they had regrets about

their treatment but some questioned whether they would have the same treatment if they were older. In a study of SCCHN, List et al. found that patient priorities were generally unrelated to patient or disease characteristics, with the exception that cure and living were of slightly lower priority and pain of higher priority to older patients compared with younger patients [46]. Older people were less inclined to focus on the future, and more inclined to make short term goals, describing survival as living to a set point in time or significant event.

Problems with eating and drinking after treatment were almost universal. For some this wasn't a particular problem and had very little impact, for others this had tremendous repercussions on their quality of life, with patients who socialised a lot around food now avoiding these types of situations altogether and socialising less. HR-QOL and psychological well-being seemed most affected for patients who had lost the most function or who were less able to return to normal activities – especially social activities.

It became clear that certain key adverse effects of treatment had quite broad ranging effects on lots of different aspects of a person's life. Mouth dryness seemed to have the most profound effects, causing problems with chewing, swallowing and taste. It also had less obvious implications, causing problems with voice, speech and the ability to exercise and sleep. An appreciation of such wider implications only became apparent because of the qualitative approach used. Furthermore the combination of multiple adverse effects of treatment seemed to have an additive detrimental effect on functioning and HR-QOL. For example many patients described a reduction in appetite during and after treatment, which was related to a number of different adverse effects of treatment; loss of sense of taste, pain, fatigue, low mood, mouth dryness, trismus, problems with teeth and difficulty swallowing. A number of patients described difficulties with sleeping; they would usually be able to get to sleep but would wake frequently with a dry mouth requiring water, they would then wake frequently to pass urine and would

then often be kept awake by worries and concerns about their cancer. These relationships – only demonstrated because I used a qualitative approach - allowed me to understand why outcomes are important to patients. HR-QOL questionnaires such as the UW-QOL ask whether patients have dry mouth, they allow us to quantify the problem but not to understand why it is important and what the wider effects are. Understanding the broad ranging effects of such outcomes ensures that important outcomes aren't missing from the comprehensive outcomes list, and further helps to prioritise research in this area.

Changes in cognitive function had the greatest implications for, and were most often described, by those in employment, and could be quite distressing at times. Changes in cognitive function are a recognised sequelae of radiotherapy to the head and neck secondary to significant radiation doses to large volumes of brain tissue [270]. IMRT has been associated with a net increase in irradiated brain volumes. This has implications for younger patients who may find such sequelae less acceptable due to the implications this may have for employment, and is an important adverse effect that should be discussed with patients prior to embarking on treatment with radiotherapy. IMRT is also associated with greater

The interviews highlighted a number of new concerns specific to patients with HPV-positive OPSCC which haven't previously been reported in the literature. Patients expressed concerns regarding adequacy of treatment because they had uncertainties about how and if HPV needed to be treated. Some questioned whether systemic treatments were required and whether leaving a tonsil increased the risk of getting a second HPV-related tonsil cancer. Many patients and carers expressed concerns about transmission of HPV in the future and some expressed concerns that their partner was responsible for their cancer or that their partner felt this way. There were anxieties about engaging in sexual activity for all patients with HPV-related OPSCC, especially oral sex, however the extent to which this limited such activities was variable. Other factors such as mouth dryness or

perceived physical deformity also played a role in stifling sexual activity. Some had misconceptions about the ease with which HPV could be transferred – possibly by a handshake alone. HPV-positivity led to concerns regarding the wider impact on the family. It became clear in these interviews that HPV is a shared concern for the patient and their spouse, and has effects for the whole family. Parents raised concerns that their children would have inherited a predisposition to HPV-related cancers, and talked about HPV vaccination. Another patient in this cohort, who had attended a patient support group in his home town, found that HPV-positivity was very embarrassing for women in particular as it was considered to be a sexually-transmitted disease. Much of this seemed to stem from media publicity surrounding the link between HPV-positive OPSCC and oral sex.

HPV-positivity, although conferring survival advantages, brought with it, for some, far wider ranging social concerns and consequences than the cancer alone did. This is an interesting area for future research, as, in current practice, we as clinicians seem to underestimate these concerns. Whilst patients were glad of a more positive prognosis, for some patients there was frustration at being made to feel they were 'lucky' that their cancer was HPV-positive. Anecdotally, such normalisation of HPV status is common, and qualitative research amongst clinicians has shown that this is regarded a key message to communicate to patients, alongside emphasizing the positive prognosis [271]. Although clinicians approach HPV-positive tumours with a more positive outlook, because of the favourable prognosis, for patients, they have cancer and, as one patient said, 'cancer is scary'. Clinicians need to be careful to acknowledge the seriousness of a cancer diagnosis; patients do not feel 'lucky' that their cancer is HPV-positive, they wish they didn't have cancer at all. These findings have important implications for clinical practice and the ways in which healthcare professionals communicate with patients with HPV-positive disease, including what information and advice are given regarding sexual encounters and HPV vaccination.

Carer accounts complemented those of patients, although they did not reveal any additional outcomes. They were often more revealing about the emotional and physical challenges of treatment. In some cases, this seemed to be due to stoicism on behalf of patients; in the combined interviews, carers would sometimes interject to paint a darker picture of the events than the patient themselves. In other cases, patients simply didn't recall certain events. It was more difficult to explore these differences in separate interviews. Carers were more focused on acute effects of treatment than late effects. This might be because they were more involved in providing care to the patient at this point in time, because the acute effects are so much more dramatic, or because pain is a significant acute issue and is distressing for others to witness. This could also appear to be the case because patients may have some recall bias about the acute events of their treatment, they are sometimes so unwell during treatment that they don't remember as much as their carers about the actual events. Another possibility is that the events are so psychologically distressing to recall and talk about that patients are motivated to minimise the effects.

Even in the presence of considerable functional deficits however, no patients expressed regret at their choice of treatment. Yet, some carers questioned whether they would have radiotherapy if ever required, or whether their partner would choose it if they had known how severe the adverse effects of treatment would be. As suggested in other research, patients might be more willing than non-patients to undergo aggressive treatments and endure acute distress in the interest of survival [266]. Although survival was prioritised by patients, the cost of this – the adverse effects of radiotherapy in particular – were less of a 'good deal' from the carers' perspective.

Carer burden was substantial, and largely related to the dependency of their partners on them during and after treatment. Role reversal was discussed by several carers. For some couples the patient had been the breadwinner and more dominant

force in the relationship. Their illness and treatment changed this; because they were unable to make household decisions or to manage finances, the dynamic of their relationship changed, which some carers found very difficult. In contrast this didn't seem to concern patients.

Concerns about recurrence were of variable prominence in peoples' accounts, and didn't seem to be related to HPV status, or the length of time since treatment, the factors which are likely to be of greatest concerns to clinicians when considering recurrence risk. Carers were more inclined to express concerns about recurrence. This seemed in some cases related to the fact that they had no control over this- they wouldn't be able to experience symptoms – and they were concerned that because their partner didn't have symptoms until later on the first time around, they may be late to pick up on a recurrence. This, however, was also a concern of several patients.

Carers had more anxiety about weight loss than patients, which seemed to stem from being told by healthcare professionals that it was their responsibility to ensure that their partner ate and maintained weight. Unfortunately, this became a source of significant friction between patients and their carers; whilst patients were often disinclined to eat, their partners were constantly encouraging this. Some patients even described a dread or fear of eating.

3.7 Conclusion

Survival is the most important outcome to patients and carers, and this was most emphasised by parents of young children and those with caring responsibilities. Anxieties around recurrence and weight loss are highest amongst carers. This qualitative study has reinforced the existing literature by showing that the adverse effects of treatment for OPSCC are severe and in many cases persistent. The implications of these effects are different for patients depending on their age,

interests, social circumstances and commitments. Long-term mouth dryness, taste disturbance and dysphagia were most troublesome to patients who had enjoyed socialising with food prior to their diagnosis. Mouth dryness has multiple broad reaching effects beyond dysphagia, and this qualitative study has illustrated the ways in which multiple adverse effects interplay to have a profoundly detrimental effect on patients' lives. This study is the first of its kind to have identified concerns specific to patients with HPV-positive OPSCC which have implications for clinical practice. A unified discussion for the thesis is presented in chapter five.

Chapter 4

A Delphi study to identify outcomes to include in a Core Outcome Set for clinical trials in Oropharyngeal Cancer

4.1 Rationale for this chapter

In this chapter I will present the results of the Delphi study, used to reach consensus on outcomes for inclusion in a Core Outcome Set for clinical trials in Oropharyngeal Cancer. This is the third and final methodological strand to the research in this thesis, which brings together the outcomes identified in the systematic review described in chapter two and the qualitative interviews described in chapter three.

4.2 Objectives

The objective of this Delphi study was to establish which outcomes a multi-stakeholder group of participants believe should be included in a core outcome set for clinical trials in OPSCC.

4.3 Methods

In conducting this study, I adhered to a predefined protocol, published in 'Trials' http://www.trialsjournal.com/content/15/1/168, see Appendix 1 [74]. Ethical approval for this study was granted in the UK by the Liverpool Central Research Ethics Committee (reference 12/NW/0708). The study was registered on the NIHR portfolio, ID 13823 (17 January 2013). Approval at MDACC (Houston, TX, US) was provided by the Institutional Review Board (IRB) (protocol number 2013-0285) for patient interviews, however permission for the Delphi study was not required because interview participants volunteered.

4.3.1 Participants

The COMET initiative advise the use of a diverse range of stakeholders in Delphi studies to reach consensus on outcomes to include in a COS. This includes patients with the condition under study and healthcare professionals with knowledge of the condition. Patients have a variety of perspectives about living with a condition, and much evidence now suggests that clinicians and researchers may not realise that certain outcomes are important to patients [272, 273]. This is especially pertinent in OPSCC where the side-effects of multi-modality treatment are profound. Patient involvement in outcome selection in other clinical areas has led to the incorporation of previously unanticipated outcomes into COS [274]. The patients' perspective helps to contextualise the condition, and this helps us to evaluate the relative importance of the different outcomes of treatment.

For the reasons discussed in the previous chapter, carers are key stakeholders and 'involved witnesses' to the patient's journey through diagnosis and treatment. They have unique perspectives and have experiential knowledge as well as expertise. The purpose of involving carers in this research was not so much to discuss the burden of treatment on them but to illuminate the patients' experience.

The primary remit of a COS is for application in clinical trials to improve the consistency of outcome measurement and thus facilitate meta-analyses. We therefore felt it was important that the clinicians involved were familiar with clinical trials and outcome assessment in this context. OPSCC is managed by a multi-disciplinary team of healthcare professionals and we therefore invited medical and surgical oncologists, speech and language therapists and cancer nurse specialists to participate. To increase the diversity of stakeholders we invited patients and healthcare professionals from the MD Anderson Cancer Center in Houston to participate in the Delphi. Patients in the UK were treated at two

different centres, and healthcare professionals were from a range of specialties from a number of different centres in England and Wales.

4.3.1.1 Eligibility criteria

Inclusion criteria

Patients

Adults, over the age of 18, who were up to 5 years following completion of treatment for OPSCC.

Carers

An individual, such as a spouse or family member, who provides informal care to the patient.

Clinicians

Clinicians working in the field of Head and Neck Cancer who were at an OPSCC clinical trial investigator meeting, comprising:

- Doctors of registrar level or above in the fields of Otolaryngology, Oral and Maxillofacial surgery, Plastic surgery or Oncology
- Speech and language therapists with a special interest in Head and Neck Cancer
- Head and Neck Cancer Nurse Specialists

Exclusion criteria

- Patients with active disease or known or suspected recurrence

- Non-English speakers

4.3.1.2 Sampling

The patients recruited from the interviews had been sampled consecutively, and latterly by purposive sampling, guided by a sampling matrix of clinical and sociodemographic characteristics. Carers were recruited by convenience sampling. Patients and carers recruited exclusively to the Delphi study were approached consecutively in survivorship clinics, and no sampling matrix was applied. This approach was taken because OPSCC still occurs in relatively small numbers and we wished to reach our recruitment target within the time limits of the study. Clinicians were sampled opportunistically, whilst adhering to the eligibility criteria. Some of the clinicians were familiar to members of the study team but the majority were not.

Interviewee participants - UK

Those who had given verbal consent at the time of interview were contacted by telephone to ask whether they would like to receive more information about the Delphi Study. If I was unable to contact participants by telephone, I would make two further attempts, and cease contact at this point if I was unable to make contact. For reasons of confidentiality I did not leave voicemail messages.

Packs containing a letter of invitation, information sheet, consent form and the first-round survey were sent by post (see appendices 10-13). Participants were asked to return these in the stamped, addressed envelope provided within two weeks. This information contained my contact details, should the participant wish to discuss the study further. If surveys were not returned within two weeks, a reminder phone call was made, and after this contact ceased if there was no response.

Interviewee participants – US

Those who had provided email addresses were invited to participate in the Delphi study. A small amount of information was sent by email with a link to more information and the online version of the survey (Appendix 14). Links were also provided to the COMET initiative website (www.comet-initiative.org) and the published protocol for the CONSENSUS study (http://www.trialsjournal.com/content/15/1/168). Participants were asked to complete the survey within two weeks of the email. Reminder emails were sent to those who failed to complete the survey in time.

New patients and carers recruited to Delphi

Eligible patients were identified and approached in survivorship clinics in Liverpool by research staff. In Sunderland, patients were identified and approached, as for the qualitative interviews by a study collaborator (JMP). Verbal information was provided about the Delphi study along with an information sheet. Participants agreeing to receive further information were asked to provide a telephone number and email or postal address. Paper packs were posted a week following the approach. If surveys were not returned within two weeks, a reminder phone call was made, and after this contact ceased if there was no response.

Clinicians – UK

The PATHOS study investigator meeting on 5th July 2014 was used to approach a large group of clinicians with a special interest in clinical trials in SCCHN. I presented the CONSENSUS study to the audience of this meeting comprising Oncologists, Head and Neck Surgeons, Speech and language therapists, Cancer Nurse Specialists and Research Nurses. I asked all eligible participants to complete surveys, which I personally distributed in hard copy during a break in the meeting. Surveys were collected upon completion at the end of this break. Some clinicians took surveys away with them and returned by post.

Clinicians – US

MD Anderson Head and Neck Oncologists, Surgeons and Speech Pathologists were invited by email to participate in the study. This email mirrored those sent to patients in that they contained a small amount of information about the study, with links to more information and the survey. One reminder email was sent to those failing to respond.

4.3.2 Study Design

4.3.3 Development of the Delphi Survey

A comprehensive list of outcomes was compiled from the outcomes identified in the systematic review described in chapter two and those extracted from the qualitative interviews described in chapter three and synthesised into a survey comprising 50 questions (Appendix 15). We wished to avoid the survey being too long, as we were concerned this would be a barrier to recruitment and retention in the second round. An overview of this process is given in figure three.

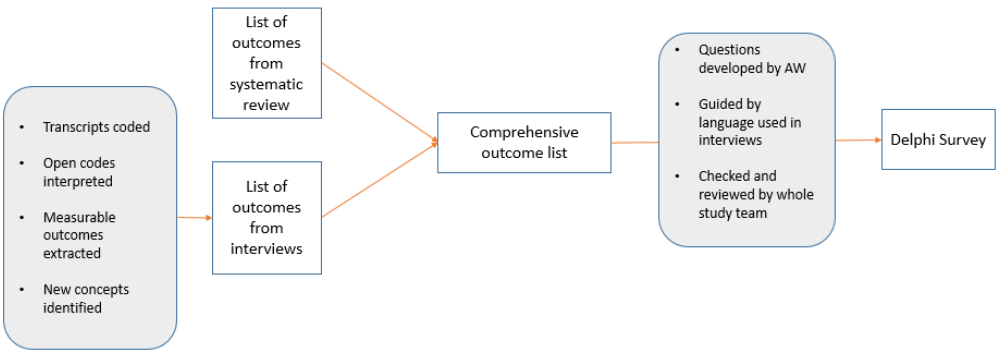


Figure 3. Overview of steps in survey development

4.3.3.1 Open questions

To avoid researchers imposing their views about items of importance on participants, a recommendation for good methodological practice in Delphi studies is that researchers begin by asking open questions, rather than presenting participants with a list of items generated by the researcher [251]. In the case of COS development, the outcomes deemed important to clinicians may not be the same as those deemed important to patients. I therefore set out to explore this uncertainty in the qualitative interviews with patients and identified key outcomes which were incorporated into the survey. Additionally, in round one, I asked participants to add any comments about the outcomes included and to add any additional outcomes and rate these.

4.3.3.2 Qualitative interviews

The qualitative interviews, described in chapter three were undertaken to identify the outcomes of importance to patients, and carers of OPSCC patients, who are major stakeholders. We anticipated that this methodology would allow us to identify previously unanticipated outcomes, help us to understand the importance of these outcomes, ensure that outcomes important to patients and carers weren't missing from the comprehensive outcomes list and identify the language used to describe outcomes to inform the Delphi survey. One-hundred-and-thirty-six possible outcomes of treatment were identified.

The language used by patients and carers to describe outcomes or events informed my use of language in the qualitative interviews, and changed at the different recruitment sites. Mirroring the language used by interviewees, showed that I was discussing things on their terms, with them as the expert, rather than using unfamiliar or bewildering medical terminology. It helped to build rapport. Whilst

some patients chose to use medical terminology, I only used this when they did so first.

Listening to the language people used helped in developing questions for the Delphi survey. Firstly, to establish which medical terms people were generally familiar with, and secondly to understand how they defined certain events. However, because I was inviting patients from different parts of the UK and the US to participate in the Delphi, I had to be careful about using 'local' terminology that might make no sense to others. Table 8 gives examples of use of patient language.

Medical terminology	**Language used by patients and carers**
Dysphagia	Difficulty swallowing
Enteral feeding	Tube feeding
Mucositis	Radiation burns
Oesophageal dilatation	Throat stretch
Osteoradionecrosis	Infection in the jaw
Xerostomia	Mouth dryness or lack of saliva

Table 8. How interviews informed language used

4.3.3.3 Systematic review

We consulted the current literature to identify the outcomes reported in clinical trials in OPSCC. We assumed that these were the most important outcomes to clinicians, as they design the studies and select the outcomes to be measured and reported. To ensure that the outcomes identified were representative of contemporary practice, I restricted the review to RCTs reported May 2003 – May 2013. Published trial reports were scrutinised, and the primary and secondary outcomes extracted, further outcomes that were reported, but not listed as

outcomes, were also extracted. Thirty distinct outcomes were carried through to the Delphi. This systematic review is reported in full in chapter two.

4.3.3.4 Comprehensive outcomes list

Outcomes from the systematic review and interviews were combined to form a comprehensive list of 154 possible outcomes of treatment. These related to response to treatment, survival, acute and late adverse effects of treatment, functioning, health-related quality of life, treatment processes and psychological well-being. There was some duplication and overlap of the outcomes identified between trials in the systematic review and between trials and the interviews. When different verbatim terms were used to describe the same outcome, such as cancer-specific survival or disease-specific survival then these were combined under the most commonly used outcome term or with a new outcome term that retained fidelity to the outcome and the events to be measured. This methodology has been used by those developing core information sets in cancer [275]. Furthermore, time-points of outcome measurement were seen more as issues of *how* to measure than *what* and so 3-year and 5-year loco-regional control were synthesised into a loco-regional control domain.

4.3.3.5 Developing questions

This survey did not simply present a list of outcomes; out of context this could be difficult for patients and carers to understand [194, 276]. We therefore developed a questionnaire type survey, with a list of 50 questions about the effects of treatments on outcomes. Previous work by Sinha et al. to develop a COS for Asthma in children informed this process [277] and the interview transcripts informed the language used to describe outcomes to patients and carers.

Some composite outcomes were avoided i.e. as local control, regional control and loco-regional control were identified in the review, questions were asked about the importance of a treatment preventing cancer coming back in the same place, in the neck or distantly. In contrast the burden of late toxicities weighed heavily on some patients, and through interpretive analysis it became apparent that the patients' concerns were not the specific intervention but the *need* for further interventions – to still be a 'patient'. From these concerns, we developed a domain entitled 'the need for further interventions as a result of treatment'.

The order in which outcomes are presented in a questionnaire has been shown to be of significance. The 'consistency effect', where items are answered in relation to responses to earlier items, has been researched for more than 50 years. To overcome this effect Bradman et al. recommend that general questions should precede specific ones [278] and Sudman et al. that questions should be grouped into topics [279]. If there is evidence that respondents have stronger opinions on some items than others McColl et al. suggest that these should be placed first [118]. As there is evidence that survival is the most important outcome to patients [46, 47, 266] we placed this at the beginning of the questionnaire alongside the outcomes identified in the systematic review related to disease control, survival and HR-QOL. The following 43 outcomes related to functioning, acute and late toxicities, complications, activities, participation, relationships and further interventions. A Delphi study to develop a COS for oesophageal cancer suggested that COS studies could be influenced by the 'consistency effect'. Participants were randomised to receive questionnaires with clinical or patient reported outcomes first. The study found that the ordering of outcomes may impact on both response rates and actual responses, subsequently impacting the final COS [197].

4.3.4 Delivery of the survey

The Delphi study comprised two rounds of voting. In the survey information, the concepts of clinical trials and COS were explained. The qualitative interviews revealed that these concepts aren't particularly intuitive and can be hard for patients and carers to understand. I reviewed the interview transcripts and discussions with patients around these issues and used this to inform the text. I endeavoured to ensure that the information provided explained the concepts in terms that could be understood by non-healthcare professionals. I took advice on this from Heather Bagley, the COMET PPI co-ordinator, who also reviewed the literature.

The survey was offered either in hard copy or via an online system, on the University of Liverpool central server. Delphi software designed for the 'Management of Otitis Media with Effusion in Cleft Palate' (MOMENT) study by information systems staff at the University of Liverpool was adapted for the CONSENSUS study [280]. I played a key role in developing this and conducted the system testing prior to launch.

All data was handled via the online system and I uploaded all hard copy surveys. Each questionnaire was double checked to ensure accurate transfer of scores. Once uploaded to this system, participants who had provided email addresses were sent the round two survey via this system.

Upon completion of the survey, the online system emailed confirmation and a note of thanks. Participants were asked to look out for the second survey which would be distributed approximately one month after the closure date for round one. Participants were provided with their unique identifier and login details for the second-round survey. On completion of round two, participants were thanked for

their involvement in the study and those who had sent hard copies were sent a handwritten letter of thanks.

4.3.4.1 Round one survey

In the first round, participants were asked to consider the importance of the different outcomes of treatment in clinical trials for OPSCC, identified from the comprehensive outcomes list, and to suggest any additional outcomes they thought were important. Participants were asked to score each of the outcomes listed, and outcomes added, using the Grading of Recommendations, Assessment, Development and Evaluations scale of 1 to 9, which is a Likert type scale [281]. The survey asked participants to rate the importance of individual outcomes, with 1 to 3 labelled 'not important', 4 to 6 labelled 'important but not critical' and 7 to 9 labelled 'critical', see figure four.

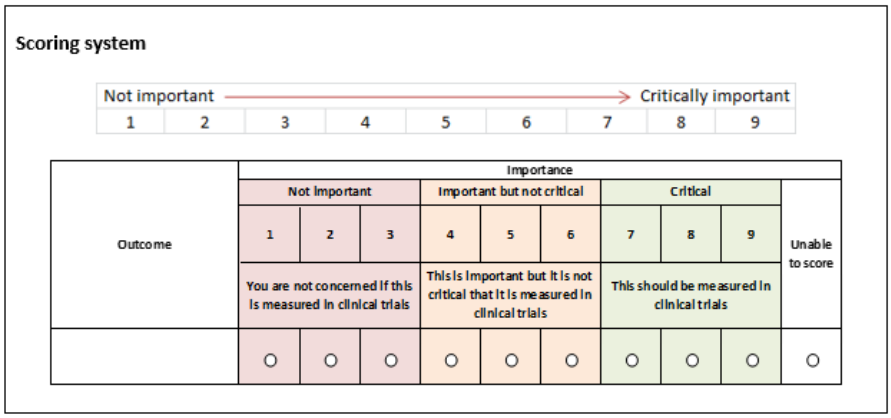


Figure 4. Scoring system for outcomes

It was acknowledged that participants may have no experience of many of the outcomes however we asked that they score how important these would be in helping them to decide between treatments. There was an 'unable to score' option.

Each outcome was presented with the medical and plain English terms and context provided with a separate explanation for some outcomes. I developed the text to contextualise outcomes, partly by reflecting on the way in which outcomes were described in the interviews. There were two surveys layouts – for patients and carers the plain English term was presented first, with the medical term below and for clinicians the medical term was presented first with the plain English term below. Anecdotal evidence suggests that clinicians participating in Delphi studies dislike being presented with lay terms. Medical terminology would however be confusing for patients and carers. This approach was therefore taken to ensure that the same information was presented to all participants, as clearly as possible.

4.3.4.2 Round two survey

In the second round, participants were asked to consider which outcomes were *core***.** The need for a COS comprising five to ten outcomes was explained, whilst acknowledging the importance of all outcomes. They were asked to reflect on how other participants had voted in the first round when re-casting their vote and the importance of completing the second round was emphasised. A proportion of participants completed the hard copy questionnaires and I uploaded these to the online system.

4.3.5 Statistical considerations

4.3.5.1 Sample size

There are currently no recommendations for the number of participants to include in a Delphi study, and there is no requirement for a statistically representative sample [282]. In a systematic review by Sinha et al. of studies using the Delphi method in COS development, the number of participants ranged from 13 to 222 [6]. We had a relatively heterogeneous group of participants and therefore felt our

sample size should be slightly larger to account for the likely diversity of opinions [24]. We also wished to have multiple panels, with participants randomised to the type of feedback they received.

4.3.5.2 Randomisation to panels

There are no methods for considering different stakeholders' views in a Delphi study, yet it is known that differences in the numbers of participant types in a Delphi study could mean the final consensus is numerically dominated by a certain cohort's responses [283]. Additionally, participants may tailor their answers to agree with a group they perceive to be more authoritative, such as clinicians [251]. Furthermore, some evidence suggests that the way Delphi participants vote is affected by their panel composition and from whom they receive feedback [284-286].

At the time of designing our study, early results from a Delphi survey reported by Macefield et al. were presented at the 2nd Clinical Trials Methodology Conference in Edinburgh [287]. This study, to develop a COS for oesophageal cancer surgery, comprising patients and clinicians, showed that patients receiving patient and clinician feedback (versus patient only feedback) rated fewer items as important whereas clinicians receiving patient and clinician feedback (versus clinician only feedback) rated more items as important. We wished to investigate this novel methodology and felt that, in a clinical area where function and quality of life – i.e. the lived experiences of a disease and its treatment - are so profound, it was important to investigate the differences between the stakeholder groups.

We therefore randomised patients and carers to a patient and carer only panel or a patient, carer and clinician panel and clinicians to a clinician only panel or the patient, carer and clinician panel. All stakeholders were given equal importance in the analysis. We planned to recruit 30 patients and carers, and 30 clinicians with a

view to having a minimum of 20 clinicians and 20 patients and carers completing the second-round survey. We approached relatively more clinicians than patients and carers because we expected attrition to be higher in this group.

Upon invitation to the Delphi, participants were assigned a unique study ID and randomised to one of the three panels, as shown in figure five. For round one, the same survey was distributed to all participants, irrespective of their panel. At invitation to round two, they were informed of their panel, and that there were other panels with different stakeholder groups.

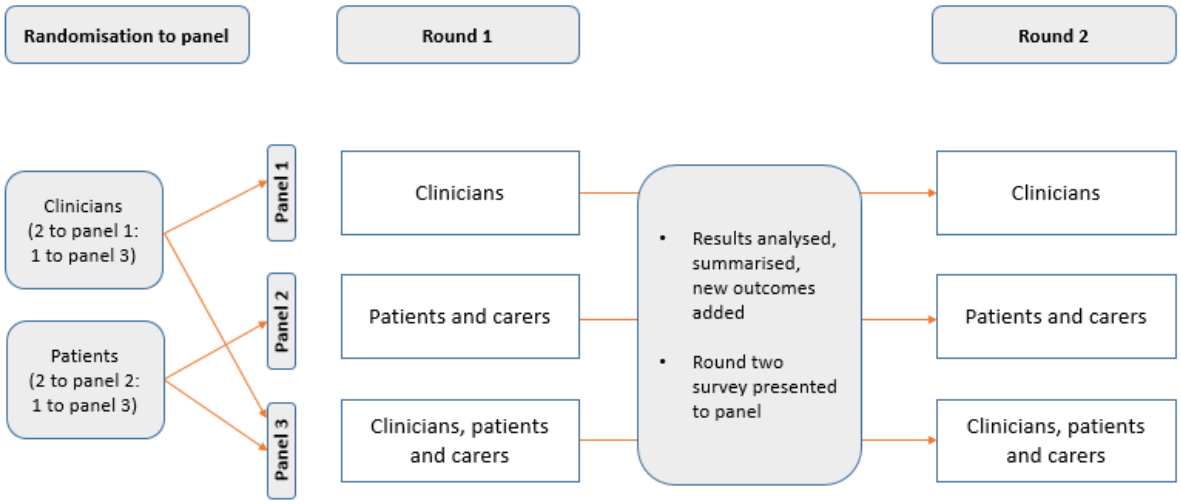


Figure 5. Allocation to panels

4.3.5.3 Randomisation method

Using sealedenvelope.com (https://www.sealedenvelope.com/) and block randomisation, participants within the patient and carer group were randomised in a 2:1 ratio to the single or combined panel and participants within the clinician group likewise to the single or combined panel. Randomisation lists were generated by a research team member not involved with recruiting participants

(CTS). The lists were concealed from the recruiting researcher (AW) throughout the process.

4.3.5.4 Minimising attrition

Minimising attrition is important in Delphi studies because people with minority opinions are more likely to drop out of the process which can lead to an overestimation of the degree of consensus in the final results [288]. In order to minimise this effect, in advance of distributing surveys, I sought verbal confirmation from participants that they would like to receive information about the study. The information provided with the survey emphasised the importance of completing both rounds, and when the second round questionnaire was distributed, this was again emphasised. Secondly, so that people didn't feel their voices weren't being heard, in the invitation for round two we acknowledged the differences in how people voted.

To identify whether there was evidence of bias introduced through participant attrition in round 2, the mean score across outcomes from round 1 was calculated for each participant and these were compared for participants completing both rounds against those completing round 1 only. A Mann-Whitney U test was used to test the hypothesis that there was no difference between the groups.

4.3.6 Anonymity

By Sinha et al.'s classification, this study was not anonymised [251]. Patient and carer pairs were invited to participate and it is possible that they would have discussed the survey and their voting. Also, for the first round, clinician participants completed the survey at a meeting with other clinicians; it is possible that they too would have discussed the survey and their voting. In the second round, all clinician participants completed the survey online. Some of the invited

participants worked together and I cannot presume that they did not discuss the survey. The patients and carers were unaware of the identities of the clinicians completing the survey and vice-versa. The identities of all participants were only known to AW and MHJ, the survey administrator.

4.3.7 Data protection

Data was handled in compliance with the Data Protection Act (1998). In accordance with the university policy for the disposal of confidential waste, hard copies of the completed surveys were destroyed once uploaded to the online Delphi system.

4.3.8 Survey launch

Round one opened on the 5th June 2014, with the clinician surveys being distributed first. Responses were requested by 19th June 2014 although completed surveys were accepted up to the point of analysis. Round two was launched on the 17th July with a closing date of 15th August, although again late completed surveys were accepted.

4.3.9 Analysis

4.3.9.1 Round one

Additional outcomes identified by participants during round one were reviewed and coded by the whole study team. Consideration was given to whether these were already included, but perhaps worded differently and whether they were clinically relevant. Those felt to be appropriate by the whole study team were added to the second-round survey. For each outcome, the number of participants who scored it and the distribution of scores (as number and percentage who scored

each outcome) was summarised by panel and stakeholder group, and this data was added to the round two survey for the respective panels, see figure six.

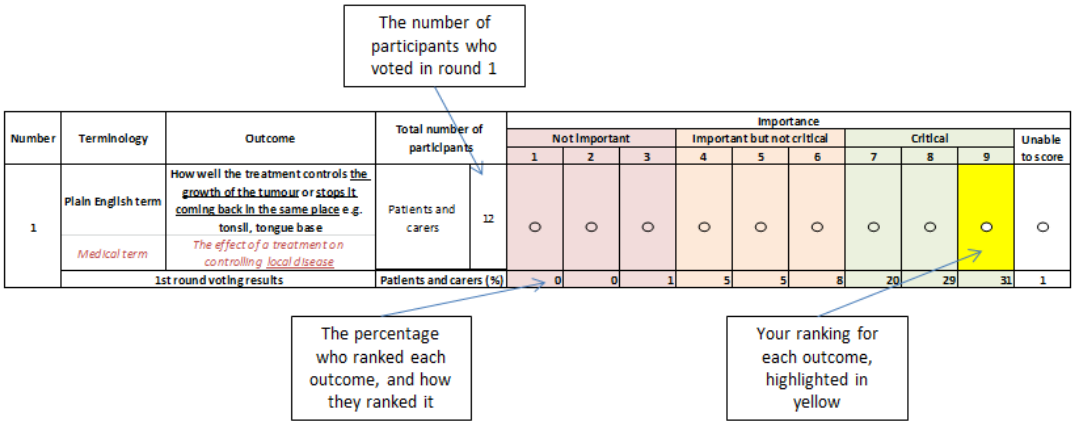


Figure 6. Layout for round two

All outcomes, irrespective of their score, were carried forward to round two. The number of respondents in each panel and stakeholder group was assessed following round one closure, and only invitees who completed round one were invited to round two.

4.3.9.2 Round two

The total number of participants completing the second-round was evaluated by panel and stakeholder group and attrition summarised by panel, stakeholder group and method of recruitment to inform future practice.

4.3.9.2.1 Definition of consensus

There are no agreed methods for selecting cut-off criteria, however, on this issue we took advice from the COMET initiative and used criteria previously implemented in the MOMENT study [280]. These criteria were defined a priori in

the published protocol for this study. Consensus to carry an outcome through to the core outcome set was reached when

- More than 70% of participants scored its importance as 7 to 9
  AND
- Fewer than 15% of participants scoring its importance as 1 to 3
  AND
- The outcome met these criteria in each panel

For each outcome, the number of participants who scored it and the distribution of scores was summarised by panel and stakeholder group, and each outcome was classified as 'consensus in', 'consensus out' or 'no consensus' according to the classification in table nine.

Consensus classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more participants scoring as 7 to 9 AND <15% participants scoring as 1 to 3
Consensus out	Consensus that outcome should not be included in the core outcomes set	70% or more participants scoring as 1 to 3 AND <15% of participants scoring as 7 to 9
No consensus	Uncertainty about importance of outcome	Anything else

Table 9 Definition of consensus (Taken, with permission from the MOMENT study [280])

A pre-defined stop criterion for this study was chosen as whichever occurred first of

- Reduction of the long list of outcomes to ten or less, or
- Completion of the second round of voting

A condition of this was that no new outcomes were suggested in round one, otherwise, a second round would have to be conducted to allow for voting on these outcomes. If consensus was not reached after round two, or there was major disagreement, we planned to conduct a face-to-face meeting of stakeholders to resolve these differences and identify consensus outcomes. At this point, if there had been disagreement about some outcomes, we would have included a smaller number of outcomes, upon which there was consensus, in the COS, as per the recommendations by Williamson et al. [152].

A one-way ANCOVA was conducted to determine whether there were differences between panels in the ranking of outcomes in round two, controlling for ranking in round one.

4.4 Results

4.4.1 Participants

In total, 37 clinicians and 43 patient and carers (31 patients and 12 carers) in the UK and US participated in the study. Clinician participants comprised Clinical Oncologists (n=13), Head and Neck surgeons (n=11), Speech and Language Therapists (n=12) and one Cancer Nurse Specialist. The patient cohort comprised 24 men and seven women, and the carer cohort comprised one man and 11 women.

4.4.2 Recruitment and attrition

To encourage participation and to try to reduce attrition, I made a telephone call to UK patient and carer interviewees in advance of distributing the letter of invitation and survey. Of the 24 interviewees, I was unable to contact five, and one declined, these were therefore not sent an invitation letter and survey. The flowchart in figure seven shows the number of stakeholders invited and randomised to each panel, and the number completing each round by panel and stakeholder group. Attrition was highest in the clinician only panel and amongst clinician stakeholders, however contrary to what I had expected, clinician attrition was proportionately higher in the combined panel compared to the clinician only panel.

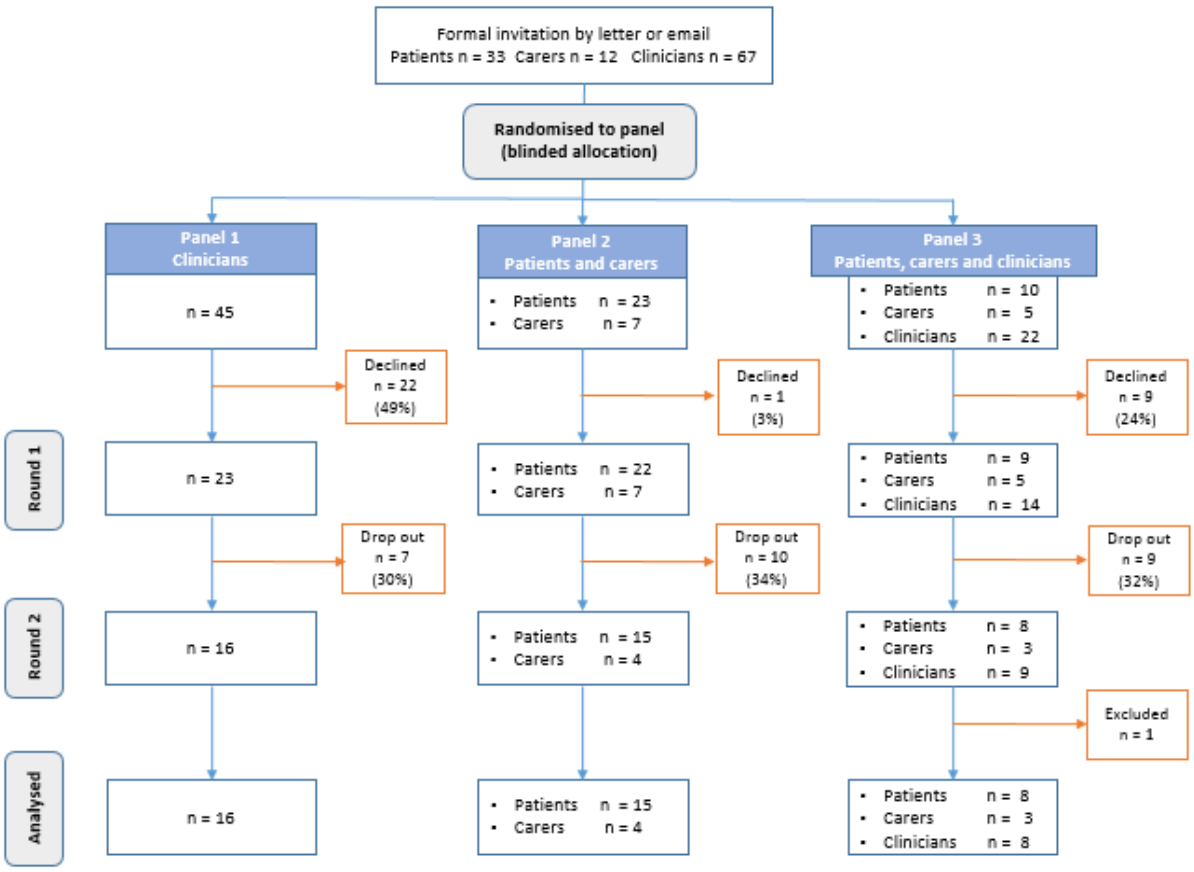


Figure 7. Recruitment and attrition by panel and stakeholder group

*One clinician participant was excluded because their survey was insufficiently completed

The breakdown of invitees and responders by country and stakeholder group, including clinician specialties is shown in table 10.

Stakeholder group	Invited	Respond round 1	Respond round 2	Analysed
UK				
Patient	27	25	18	18
Carer	12	12	7	7
Clinical Oncologist	13	12	7	7
Head and Neck Surgeon	9	9	7	6
Speech and Language Therapist	11	11	9	9
Cancer Nurse Specialist	7	1	1	1
US				
Patient	6	6	5	5
Clinical Oncologist	11	1	0	0
Head and Neck Surgeon	11	2	0	0
Oral oncology and maxillofacial prosthodontics	3	0	0	0
Speech pathologist	2	1	1	1

Table 10. Invitation and participation by country and stakeholder group

NB. Round two responders were a subset of round one responders. No new participants invited to round two.

4.4.2.1 Factors affecting attrition

The method of approach had a significant impact upon response rates in the first round amongst clinicians, with 93.9% of those responding to a face to face approach (31/33), and only 17.6% responding to an emailed invitation (6/34).

Response rates were high amongst patients and carers, with 100.0% response to postal invitation (37/37) and 75.0% response rate to email (6/8) in the first round. The patients and carers who participated in the interviews were more likely to complete both rounds, with 90.5% (19/21) completing versus 45.5% (10/22) of those patients and carers recruited exclusively to the Delphi. When making reminder phone calls, one of these patients commented that she didn't think it would be an 'ongoing thing'.

Those clinicians who failed to participate in round two were not approached to ask their reasons for this, however, from our online software we know that few logged in to complete round two. It would therefore seem that the way in which outcomes were presented, or the perception of having minority views did not contribute to their attrition as they wouldn't have known how others ranked outcomes without logging in to the online system.

Attrition was higher amongst clinicians, and highest in the US cohort of clinicians, with only one completing both rounds. US clinicians did not have minority views; average scores were similar to those of UK clinicians (US 6.5, UK 6.3) and all of the outcomes that reached consensus for UK clinicians in round one, reached consensus in the US clinician cohort.

4.4.2.2 Impact of attrition

Nearly a third of participants (32.5%) dropped out between rounds one and two. The number of participants remaining in each panel, remained roughly equal, with 16 participants in panel one, 19 in panel two and 19 in panel three. The proportion of clinicians to patients and carers across all panels remained stable at 1:1.2 in round one and 1:1.25 in round two.

4.4.2.3 Attrition bias

The mean score across outcomes from round one was calculated for each participant and then compared between the groups of participants that completed one round only and those that completed both rounds. There was no significant difference in the mean round one scores for those completing both rounds (n=54, median 6.42, IQR 5.6 to 7.3) versus those completing round one alone (n=26, median 7, IQR 5.9 to 7.7), p=0.153. It is possible however that the lack of significant difference is due to small numbers.

4.4.3 Incomplete surveys and excluded participants

Two participants in panel one and one participant in panel three failed to fully complete the second round of the survey. The two participants in panel one ranked 49 and 54 outcomes. These cases were discussed with the study team and it was decided to keep their answers for analysis. The participant in panel three had only ranked five outcomes however and was therefore excluded from the analysis. A patient in panel two had selected "unable to comment" for 40 of the outcomes, when I spoke to her about this she had been told by research staff to only rank outcomes that had affected her (despite ranking all outcomes in round one) her rankings were included but the 'unable to comment' rankings were excluded from the second-round analysis.

4.4.4 New outcomes

Participants were asked to add and rank any outcomes that they thought were missing from the Delphi in round one. Outcomes were only added if there was consensus amongst the whole study team. Twenty additional suggestions were made by three clinicians and six patients. Eighteen of these were unique suggestions. Of these, eight suggestions were felt to have been already included in the existing questions, four were not felt to be appropriate and were excluded and

six new outcomes were added for round two. The first four listed below were from clinicians, the last two from patients, these were:

- The need for dentures
- Producing too much saliva
- The impact of a treatment on earnings/ finances
- The inconvenience of a treatment i.e. time spent travelling to and from medical institutions for treatment
- The requirement for ongoing or long-term dental care
- The impact of a treatment on concerns about the cancer returning

Participants were informed of the new outcomes and asked to rank these alongside the other outcomes in round two. These are shown in table 11, overleaf.

Patients	Clinicians

Longterm impact on future morbidity (Is that a lump)	Hypernasality
Long term problems with teeth - how can they be fixed when my mouth hardly opens. As for Q27 but more of a worry for the future	Wearing obturator
Being informed of after effects of cancer treatment before treatment	Wearing dentures
Help to fill in benefit forms	Pain on swallow
Dental care afterwards	Excess salivation
Prior info on the likelyhood of side effects post treatment*	Speech
Prior info on the likelehood of side effects after treatment*	Voice
Fatigue	Talking on telephone
Nerve damage to shoulder	Solid vs soft diet
	Effect on earnings/ finances
	Time spent on treatment/ transport/ managing toxicity

Table 11. Additional outcomes suggested by Delphi participants in round one (verbatim)

*This comment was made by a patient and carer pair which suggests they completed their surveys together

4.4.5 Voting

Appendix 16 shows the distribution of scores for each outcome by panel and round.

4.4.5.1 Variability in voting between panels

There was substantial coherence between panels, with six outcomes achieving consensus in round one and maintaining consensus in round two across all panels. There was more heterogeneity amongst patients and carers; the patient and carer only panel had the highest number of outcomes reaching cut-off (n=15), and, when panel three was analysed for patients and carers there was a higher number of outcomes that met the cut-off selected by patients and carers than by clinicians (17 outcomes for patients and carers versus 12 for clinicians).

4.4.5.2 Variability in rankings between rounds

The average percentage change in scores between rounds was 12.1% in panel one, 8.7% in panel two, and 17.9% in panel three (8.9% clinicians, 24.5% patients and carers). Across all panels there was greater change amongst patients and carers in their voting, however this was most pronounced in the combined panel. This suggests that patients and carers were influenced by clinicians but that clinicians weren't influenced by patients and carers.

4.4.5.3 Analysis by clinical characteristics

There was strong consensus on a core of 5 outcomes for patients with positive, negative and unknown HPV status that also reached final consensus and were included in the COS. There was no correlation between mean score and age (r = -0.172, p=0.433). This was not particularly surprising as the qualitative interviews had suggested that whilst the emphasis placed on some outcomes was greater in younger patients, the same outcomes were still important.

4.4.5.4 Variability in outcomes achieving consensus between rounds

The number of outcomes meeting the pre-defined cut-off increased from round one to round two, as shown in table 12. This was only accounted for by one of the new outcomes, which met cut-off in the patient only group.

	Round 1	Round 2
Panel 1	8	11 (3 added)
Panel 2	12	15 (1 dropped, 4 added)
Panel 3	10	12 (2 added)

Table 12. Number of outcomes reaching consensus by panel and by round

There were eight common outcomes that met the cut-off across all panels in round two, with four outcomes reaching cut-off in two panels and six meeting the cut-off in one panel (table 13). By our method of consensus (including outcomes that reached consensus in each panel) we could have stopped the study following the first round, as 6 outcomes met this criterion. Additional outcomes were suggested and added however so we had to proceed to the second round to see how participants ranked these.

Outcome	Panel 1	Panel 2	Panel 3	
The effect of a treatment on controlling local disease	•	•	•	Core Outcome Set
The effect of a treatment on controlling regional disease	•	•	•	
The effect of a treatment on controlling distant disease	•	•	•	
The effect of a treatment in preventing death from cancer	•	•	•	
The risk of death from treatment	•	•	•	
The effect of a treatment on health-related quality of life	•	•	•	
The need for additional surgery or invasive procedures as a consequence of treatment (e.g. Tracheostomy, dilatations, further reconstructive surgery)	•	•	•	
The risk of long-term dysphagia associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)	•	•	•	
The effect of a treatment on the risk of death from any cause		•	•	
The effect of a treatment on the need for long-term regular enterostomy tube feeding	•		•	
The long-term effect of a treatment on the ability to breath normally	•		•	
The risk of long-term osteoradionecrosis associated with treatment	•	•		
The requirement for supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy)		•		
The long-term effect of a treatment on memory and cognition		•		
The long-term impact of a treatment on psychological well-being			•	
The long-term impact of a treatment on the ability to return to work		•		
The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)		•		
The impact of a treatment on concerns about the cancer returning		•		

Table 13. Consensus outcomes in round two

4.4.5.5 Outcomes reaching consensus by stakeholder group

When analysed by stakeholder group there was significant heterogeneity in the numbers of outcomes reaching consensus (see table 14). This ranged from 9 outcomes amongst head and neck surgeons to 29 outcomes amongst carers. Again, this was not entirely surprising as during the interviews carers tended to place greater emphasis on the morbidity associated with treatment, with some saying they wouldn't have radiotherapy if they were in the patient's shoes. Unfortunately this suggests that carers didn't appreciate the need to identify a core set of a smaller number of outcomes. One patient, when providing feedback on the Delphi shed light on why they may have struggled to rate a smaller number of outcomes as important, saying that they were all critical at one point in time during or after treatment.

Long-term dysphagia, enteral feeding, and the ability to breath normally reached consensus amongst all stakeholder groups, but patients.

	Outcome	Carers	Speech and language therapists	Patients	Medical/ radiation oncologists	Surgical oncologists
1	The effect of a treatment on controlling local disease	*	*	*	*	*
2	The effect of a treatment on controlling regional disease	*	*	*	*	*
3	The effect of a treatment on controlling distant disease	*	*	*	*	*
4	The effect of a treatment in preventing death from cancer	*	*	*	*	*
5	The risk of death from treatment	*	*	*	*	*
7	The effect of a treatment on health-related quality of life	*	*	*	*	*
6	The effect of a treatment on the risk of death from any cause	*	*	*	*	
17	The risk of long-term dysphagia associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)	*	*		*	*
18	The effect of a treatment on the need for long-term regular enterostomy tube feeding	*	*		*	*
24	The long-term effect of a treatment on the ability to breath normally	*	*		*	*
26	The risk of long-term osteoradionecrosis associated with treatment	*	*	*	*	
9	The requirement for supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy)	*		*		
10	The need for additional surgery or invasive procedures as a consequence of treatment (e.g. Tracheostomy, dilatations, further reconstructive surgery)		*	*		
11	The incidence and severity of early side-effects associated with a treatment (e.g. acute toxicities or complications)	*	*			
19	The long-term effect of a treatment on being able to/ wanting to eat or drink in public and take part in social occasions involving food	*	*			
41	The long-term effect of a treatment on memory and cognition	*		*		
48	The long-term impact of a treatment on the ability to return to work	*	*			
56	The impact of a treatment on concerns about the cancer returning	*		*		
12	Having to go into hospital to help deal with side-effects during treatment or when recovering from treatment	*				
14	The long-term risk of altered cosmesis, physical deformity or disfigurement associated with treatment	*				
22	The long-term impact of a treatment on the enjoyment of food		*			
23	The risk of long-term oral ulcers associated with treatment	*				
25	The risk of long-term xerostomia and altered secretions associated with a treatment	*				
27	The risk of long-term trismus or pain in the jaw associated with treatment	*				
28	The long-term impact of a treatment on tongue movement	*				
29	The long-term impact of a treatment on speech and voice		*			
30	The long-term impact of a treatment on sensation in the mouth and throat	*				
31	The long-term impact of a treatment on the integrity of the oral mucosa and lips	*				
42	The long-term impact of a treatment on psychological well-being	*				
43	The long-term impact of a treatment on sleep	*				
50	The long-term impact of a treatment on relationships (e.g. emotional, physical and sexual relationship with spouse or partner and relationships with other people)	*				
53	The impact of a treatment on earnings/ finances	*				

Table 14. Outcomes reaching consensus by stakeholder group

4.4.5.6 UK versus US patients

There was strong consensus between UK and US patients. Again, the first five outcomes reached consensus. Fourteen outcomes reached consensus in the US cohort, seventeen reached consensus in the UK cohort. Twelve outcomes were the same amongst both groups (see table 15).

	Outcome	UK	US
1	The effect of a treatment on controlling local disease	*	*
2	The effect of a treatment on controlling regional disease	*	*
3	The effect of a treatment on controlling distant disease	*	*
4	The effect of a treatment in preventing death from cancer	*	*
5	The risk of death from treatment	*	*
6	The effect of a treatment on the risk of death from any cause	*	*
7	The effect of a treatment on health-related quality of life	*	*
9	The requirement for supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy)	*	*
26	The risk of long-term osteoradionecrosis associated with treatment	*	*
41	The long-term effect of a treatment on memory and cognition	*	*
42	The long-term impact of a treatment on psychological well-being	*	*
49	The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)	*	*
10	The need for additional surgery or invasive procedures as a consequence of treatment (e.g. Tracheostomy, dilatations, further reconstructive surgery)	*	
17	The risk of long-term dysphagia associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)		*
24	The long-term effect of a treatment on the ability to breath normally	*	
48	The long-term impact of a treatment on the ability to return to work	*	
50	The long-term impact of a treatment on relationships (e.g. emotional, physical and sexual relationship with spouse or partner and relationships with other people)		*
53	The impact of a treatment on earnings/ finances	*	
56	The impact of a treatment on concerns about the cancer returning	*	

Table 15. Outcomes reaching consensus; UK versus US patients

4.4.6 Outcomes to be included in the COS

Consensus across all panels was used to define the COS, with eight outcomes reaching consensus in each panel, see table 16 for how the Delphi descriptions relate to commonly used nomenclature. The outcomes reaching consensus related to disease control (local control, regional control and distant control), survival (preventing death from cancer and treatment), health-related quality of life and dysphagia.

Delphi outcome description		Outcome
Medical terminology	**Plain English**	
The effect of a treatment on controlling local disease	How well the treatment stops the cancer coming back in the same place e.g. tonsil, tongue base	Local control
The effect of a treatment on controlling regional disease	How well the treatment stops the cancer coming back in the lymph nodes in the neck	Regional control
The effect of a treatment on controlling distant disease	How well the treatment stops the cancer coming back in other parts of the body e.g. lungs, brain, liver	Distant metastatic control
The effect of a treatment in preventing death from cancer	How well the treatment prevents death from cancer	Disease-specific survival
The risk of death from treatment	Some treatments are very toxic and carry a risk of death, how important is it that this risk from treatment is measured?	Death related to treatment (Grade 5 adverse event)
The effect of a treatment on health-related quality of life	The impact of a treatment on general quality of life	Health-related quality of life
The need for additional surgery or invasive procedures as a consequence of treatment (e.g. Tracheostomy, dilatations, further reconstructive surgery)	Needing more surgery or invasive procedures because of the treatment e.g. throat stretches, further surgery to treat complications	Interventions for the management of treatment-related morbidity
The risk of long-term dysphagia associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis	The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)	Dysphagia

Table 16. The Core Outcome Set

4.4.7 Content validation and additional comments

Feedback was sought on the process in the comments section of the survey in both rounds and informally by email correspondence with the participants. In an email to me about the study, one patient participant, who had also been a US interviewee commented:

> *"This is the first time I have seen all of my annoying side effects from chemo/radiation in one list!"*

Indeed, several participants, both patients and clinicians commented that all of the outcomes were important at one time or another, which made prioritizing these difficult:

> *"[I] don't think my survey helped very much. I could not just have a top 5 items since all side effects are equally aggravating!"*

From the interviews, we established that different outcomes take priority at different times; at diagnosis, most patients admitted to only being focused on survival. As the time since treatment lengthens and the likelihood of survival increases, participants became more concerned about the long-term adverse effects of treatment, and less focused on recurrence, although this was quite variable between participants. The adverse effects of treatment also change as time goes by, and for OPSCC patients it is likely that different outcomes are 'core' at different times.

4.5 Discussion

4.5.1 Key findings

Following two rounds of voting, eight outcomes reached our pre-defined consensus cut-off for inclusion in the COS. Local control, regional control, distant metastatic control, disease-specific survival, death related to treatment, HR-QOL, interventions for the management of treatment-related morbidity and dysphagia were the eight outcomes that reached consensus in each panel. Further outcomes reached consensus in the individual panels, however these were not taken forward as per our previously defined and published cut-off criteria [74].

Overall survival did not make the COS as it did not reach consensus in the healthcare professional panel. It was not presented as 'overall survival' verbatim, rather as 'The effect of a treatment on the risk of death from any cause'. The reasons for this are not known. It is possible that it was misinterpreted by healthcare professionals, however if this was the case I would have expected its absence to have been commented upon when asked for additional outcomes of importance in the first round. The results suggest that clinicians valued disease-specific survival over overall survival. Analysis by stakeholder group showed that the only group in which it didn't reach consensus was surgical oncologists. A COS does not prescribe that only the outcomes it includes are measured, but rather these are the minimum. We would recommend that overall survival is measured in clinical trials in OPSCC. The relative priority this takes amongst different healthcare professionals may be worthy of further investigation.

Patients and carers showed the least certainty about which outcomes were core by rating more outcomes of critical importance than healthcare professionals. When analysed by stakeholder group however, carers (29 outcomes) and speech and language therapists (17 outcomes) showed the least certainty about which

outcomes were core with patients retaining 12 outcomes and surgical oncologists rating the fewest outcomes as critical and for inclusion in the COS (9 outcomes). Panel allocation did seem to affect the way in which patients and carers voted as the greatest change in voting between the rounds was amongst patients and carers in the combined panel. As discussed in the previous chapter, it is an assumption that higher scoring of more outcomes reflects uncertainty about the purposes of the Delphi study, it is possible that this reflects the significant challenges of selecting core outcomes in conditions with high levels of morbidity. As several patients and carers told us when providing feedback on the Delphi – different outcomes are important at different times. Recent evidence in the development of COS suggests that patients are more likely than health professionals to rate an outcome as essential; three studies found that the average score awarded to outcomes in the round one questionnaire was greater for patients than health professionals [289]. This is an important consideration in the analysis; patients may be more likely to influence a core set if outcome scores are simply combined across stakeholder groups.

Several important outcomes from the interviews did not make it into the COS. Mouth dryness, taste disturbance and fatigue were repeatedly discussed by patients and carers, yet these did not make the COS. Only 63.2% (panel 2) and 63.6% (panel 3) of patients and carers ranked mouth dryness as critical, 42.1% (panel 2) and 27.3% (panel 3) ranked taste as critical and 52.6% (panel 2) and 27.3% (panel 3) ranked fatigue as critical. Research into patient concerns and the problems they would like to discuss in clinic consultations by Rogers et al. [290] supports the findings from the qualitative study that these outcomes are important. Over a third of patients attending outpatient clinics wished to discuss mouth dryness and a fifth fatigue. Long-term dysphagia, enteral feeding and the ability to breath normally reached consensus amongst all stakeholder groups, except patients. I think these outcomes are important to patients, however I think it is likely that these findings reflect the greater emphasis that patients place on survival and outcomes relating to

disease control than other stakeholders i.e. although these outcomes are important they are not *core*.

Concerns about recurrence were frequently discussed in the interviews. This wasn't included in the first round of the Delphi as a possible outcome, because we didn't consider this to be a treatment outcome. However, a patient listed 'concerns about the cancer returning' as an additional outcome in round one of the Delphi. This caused the study team to re-consider this as a possible outcome and we decided to add it to the round two questionnaire. Although it didn't reach consensus overall, it did amongst patient stakeholders. It is possible that different treatments will have different effects upon patient concerns regarding recurrence. Several patients discussed reminders of treatment in the interviews; it is possible that less invasive or less radical treatments or those associated with fewer long-term adverse effects may be associated with fewer concerns about recurrence because there are fewer psychological and physical sequelae of treatment. There is a relatively high risk of recurrence with SCCHN, especially in the first two years, and follow-up appointments are therefore frequent in this time. In the UK, patients are only discharged from routine follow-up at five years. Patients and carers in the qualitative interviews admitted that concerns about recurrence were most prominent in the days leading up to a follow-up appointment. The frequency of outpatient follow-up may therefore exacerbate these concerns. HR-QOL studies frequently point to 'fear of recurrence' as a pressing concern for patients. Rogers et al. identified this as a concern for patients in an audit of the patient concerns inventory (PCI). One-thousand-one-hundred-and-ninety-eight inventories were completed by 386 head and neck cancer survivors between 1 August 2007 and 10 December 2014 at University Hospital Aintree, one of the sites for our patient and carer recruitment. Fear of recurrence was the second most common (33%) patient concern for discussion at follow-up clinic consultations. The PCI is completed whilst patients wait to be seen in the outpatient clinic and allows the consultation to be directed towards a patient's individual concerns. Given that concerns regarding

recurrence are highest at this point, it is possible that the PCI results aren't reflective of the prominence of this amongst patient's concerns the rest of the time. One patient was concerned about recurrence in his remaining tonsil, having had one removed for HPV-related cancer. Whilst there is less morbidity associated with removing one tonsil, his anxiety related to this being a site of recurrence was high. The trade-off hypothesis has been described in breast cancer. This hypothesis proposes that breast preservation may enhance a patient's body image, but increase their fears of recurrence. Some studies have suggested that mastectomy patients felt more confident that their cancer had been cured and less concerned about recurrence compared with women receiving conservative treatment, however other studies have shown difference in recurrence fears between lumpectomy and mastectomy patients. Hilton et al. found that appraisal of the threat of recurrence was positively related to the extent of the cancer and negatively related to age. For many patients and carers in our interview cohort, concerns about recurrence seemed to be related to the insidious nature of their disease. Most patients presented with locally advanced disease and had concerns that they wouldn't be aware of their cancer recurring until it was advanced. Wong et al. found that uncertainty surrounding the effectiveness of treatment was positively related with anxiety. In this cohort, concerns about recurrence were more often expressed by patients who had a negative relationship with their treating team – which most often related to dissatisfaction with their treatment and unmet expectations. Concerns about recurrence were more prominent in the accounts of carers, which seemed related to uncertainty that they would be able to identify recurrence in their partner.

Although there was consensus on a core of eight outcomes, the different panels identified additional outcomes of importance. Had we chosen to carry forward outcomes reaching consensus in every panel, we would have had 19 outcomes at the end of the second round of the Delphi survey. Some COS Delphi studies have prioritised the patients' perspective such that their voting carries more weight in

the final consensus than that of clinicians [200]. The approach taken in this study is similar to that described by Wylde et al. [205] in which outcomes had to reach a pre-defined consensus definition in each panel to make the COS, we felt that this was more demonstrative of multi-panel consensus.

4.5.2 Nomenclature

In the Delphi study, I largely took the approach of presenting specific outcomes as questions rather than outcome 'domains' which have been used in other studies. I felt this approach would lessen ambiguity in the interpretation of the outcomes by participants, but also in interpretation of the final published COS by those using it. I felt it likely that a long questionnaire or repeated rounds of voting would be significantly burdensome enough to participants to deter them. There was therefore a requirement to be pragmatic, and thus have enough questions to include all of the outcomes identified in the earlier part of the study but not be so burdensome to discourage participation in subsequent rounds. Furthermore, some of the descriptions of areas of concern for patients related to broader domains. We therefore combined some outcomes into broader domains, such as 'the need for further interventions as a result of treatment'. The resultant problem with this however was that in wording the question about this outcome, I gave examples to illustrate possible further interventions. It is not possible to know, without directly questioning the participants, whether they believed that further interventions were an important outcome or whether the specific examples given were (see table 17). In any case the need for further interventions was deemed a critically important outcome and further research will be required to establish which further intervention(s) are important.

Plain English term	Medical term	Possible outcomes
Needing additional	The requirement for	Painkillers/ analgesics

treatments to get a person through the cancer treatment e.g. painkillers, tube feeding, tracheostomy	supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy)	Antibiotics Tube feeding Tracheostomy
The need for additional surgery or invasive procedures as a consequence of treatment (e.g. pharyngeal dilatations, further reconstructive surgery)	Needing more surgery or invasive procedures because of the treatment e.g. throat stretches, further surgery to treat complications	Dilatations/throat stretches Further reconstructive surgery Further surgery to treat complications

Table 17. Outcome domains

The language used to describe outcomes not only differs between patients, carers and healthcare professionals but even between patients and between healthcare professionals. For transparency and to try and ensure fidelity with the proposed outcome, plain English and medical terminology was used to describe all outcomes, it is difficult to know how exactly these were interpreted by patients and clinicians. Several broader outcomes arose from the qualitative interviews which I felt the need to expand upon when describing in the Delphi. For example, the need for further interventions with examples as throat stretches, tracheostomy. It is harder to know whether giving examples helped illustrate what the outcome meant or whether, because of the examples, the outcomes were open to greater interpretation, which may differ between participants.

4.5.3 Consensus meeting

A decision had been made a priori that a face-to-face consensus meeting would not be required if the Delphi reached consensus on 10 outcomes or less. The Delphi reached consensus on eight outcomes in the second round of the survey, and so the meeting was not conducted. Furthermore, resource limitations meant that this was not possible. There are benefits of face-to-face meetings however; this would have allowed us to explore the reasons why patients and carers ranked more outcomes highly and why important outcomes from the interviews did not reach consensus in the Delphi. We could also have sought feedback on the outcomes reaching consensus and whether these were felt to be the most appropriate, explored differences between the panels and the factors that influenced people to change the way they voted. I think this is an important consideration for future COS developers.

4.6 Conclusion

This Delphi study used robust consensus methodology to ratify eight outcomes to be included in a core outcome set for clinical trials in oropharyngeal cancer. Survival was prioritised by patients, carers and clinicians, corroborating other research into patient priorities in head and neck cancer [46, 174, 291]. The relatively small final sample size did not allow for any firm conclusions to be drawn regarding the effect of individual patient, carer or clinician characteristics or demographics upon outcomes of importance, however this is the first study to assess COS priorities in a cohort of HPV-positive OPSCC patients. Survival and outcomes relating to disease control were universally prioritised by OPSCC patients, carers and healthcare professionals. Swallowing was the only functional outcome to reach consensus, however there is a strong correlation between HR-QOL and function [292]. A unified discussion for the thesis is presented in chapter five.

Chapter 5
Main Discussion

5.1 Rationale for this chapter

In this chapter I will discuss the context and rationale for this research, summarise my key findings and critically evaluate the study in the context of the current literature.

5.2 Context and rationale for this research

It is widely recognised that overall survival is the gold standard end point for assessing the effectiveness of interventions in clinical trials in oncology [96], that attention should be paid to the measurement of outcomes relating to disease response, the acute and long-term adverse effects of therapy [144] and a patient's HR-QOL [239]. However important outcomes are measured inconsistently and/or defined and measured with heterogeneity that compromises data synthesis between otherwise comparable trials. Furthermore, although some outcomes may be of interest to the researcher, they may have little relevance to patients and clinical practice. High quality evidence to inform clinical guidelines and healthcare policy is therefore lacking for many interventions and areas of healthcare [77].

Methodological standards for conduct and reporting have the potential to improve the quality of data arising from clinical trials, yet this relies on adherence to such standards, and there is evidence that uptake is slow and that these may be only partially adhered to [159, 293]. Much work is therefore required to ensure uptake of such standards if they are to influence the quality of data arising from trials and thus the evidence base.

There are challenges in assessing the effectiveness of interventions for the treatment of OPSCC, because this includes surgical interventions. To date, there has been no head to head comparison of surgical and non-surgical interventions [60]. For OPSCC, chemoradiotherapy (non-surgical intervention) is considered the current standard of care [2, 58], however there is growing interest in the use of minimally invasive surgical techniques (trans-oral laser and trans-oral robotic surgery) which some believe result in better functional outcomes, whilst preserving oncological outcomes [67-69]. Furthermore, de-escalation strategies for patients with HPV-positive OPSCC have led to a significant increase in the number of clinical trials in OPSCC. The application of stringent methodological standards to trials of these interventions would allow for more accurate and timely conclusions to be drawn regarding the comparative effectiveness of interventions, it would also go some way to reducing bias in these studies.

With these concerns in mind, I set out to develop a COS for clinical trials in OPSCC what should be clinically relevant and measure outcomes that are important to patients. My ultimate goal was to improve the consistency of outcome selection and reporting, thus improving the quality of evidence regarding the effectiveness of interventions in for the treatment of OPSCC. At the beginning of this research in 2011 there were no published guidelines on COS development, and so I worked closely with colleagues within and affiliated with the COMET initiative and the MRC hubs for trials methodology research to ensure best practice. Key to our methodology was the involvement of major stakeholders in the COS development process. There were no other COS studies for SCCHN or OPSCC at this point, and no studies had asked patients about which outcomes they thought were important in the clinical trials context. One study making suggestions about OMI's for use in SCCHN clinical trials failed to consult patients when deciding which outcomes should be measured [190]. My intention was that the COS would apply to clinical trials of all contemporary interventions for the curative treatment of OPSCC, and be published in an open access journal to

increase exposure and awareness of the COS. I understood that ongoing work would be needed to validate and refine the outcomes included, with the expectation that this would change over time, as new treatments became available. I would also need to identify suitable ways of measuring the included outcomes, and make recommendations regarding this through work with COSMIN, after publication of the COS. The methodology employed and the rationale for this is discussed within the body of the thesis. This is methodological research in a relatively new area and the work within this thesis has contributed to COS development guidance [117, 194].

5.3 Summary of key findings

In the systematic review described in chapter two, I identified 58 distinct outcomes reported in 43 RCTs with a total of 259 outcomes measured across all studies and a mean number of 6 outcomes per study (range 2-12). In order, acute toxicity, overall survival, late toxicity, loco-regional control, response, disease-free survival, progression-free survival, HR-QOL, distant metastases and local control were the ten most commonly measured outcomes. Outcomes brought forward to the comprehensive outcomes list could be categorised under broader domains relating to toxicity, disease control, survival and HR-QOL. Only 6 studies (14%) provided a definition of every outcome in the trial. Of all outcomes, 58.3% (151/259) were defined. Overall survival, despite being the most common primary outcome, was only defined in 46% (18/39) of studies. HR-QOL was only measured in 7 studies, and often separately to the trial report.

In chapter three I present the findings of the qualitative interviews. The objective of the interviews was to identify outcomes of importance to patient and carers, thus ensuring that the comprehensive outcomes list did not miss any outcomes which were important to these stakeholders. Thirty-one interviews were conducted with 23 patients (17 male and 6 female) and 11 carers (1 male and 10 female)

identifying 136 distinct outcomes. These predominantly related to HR-QOL, function, toxicity and the wider impact of adverse effects on a person's ability to participate in life as before. However, as in previous research into patient priorities in SCCHN, survival was the most important outcome.

The outcomes list from these two strands of the study were combined to form a comprehensive list of 154 outcomes. A questionnaire comprising 50 questions relating to these outcomes was developed by our study team comprising two clinicians, a qualitative researcher and trials methodologist. We presented the outcomes in the context of whether these would help someone decide between treatments. Separate questionnaires were developed for healthcare professionals, patients and carers and after the first round, participants were randomised to the type of feedback they received in a nested methodological study to investigate the impact of who feedback is received from.

Following two rounds of voting, consensus was reached on eight outcomes for inclusion in the COS, namely local control, regional control, distant metastatic control, disease-specific survival, death related to treatment, HR-QOL, interventions for the management of treatment-related morbidity and dysphagia.

5.4 Appraisal of the COS

The WHO stated in 1981 that clinical trials in oncology should, as a minimum, measure the response of the tumour and metastases, duration of response to treatment and acute and long-term adverse effects of therapy [144]. The COS includes outcomes relating to response of the tumour and metastases (local control, regional control, distant metastatic control) which are in current use rigidly defined by criteria for tumour shrinkage [98, 99] and frequently used to assess the benefit of systemic chemotherapy. The duration of response was not included as a separate outcome in the Delphi. This will be an important consideration for future research

arising from the work in this thesis when making recommendations for *how* the COS outcomes are measured.

It is widely recognised that overall survival is the gold standard end point for assessing the effectiveness of interventions in clinical trials in oncology [96] and criticism has been levelled at the use of surrogates for overall survival in clinical trials in oncology, when these have been shown to have little correlation in the long-term [94]. Loco-regional control, is one such surrogate frequently used in clinical trials of OPSCC. It is a composite of local and regional control, two of the outcomes in the COS. In contrast to other areas of oncology, loco-regional control has been shown to have a strong association with overall survival in SCCHN. In 116 treatment comparisons for 22,744 patients, Michiels et al. showed that for radiotherapy treatment, effects on both duration of loco-regional control and event-free survival were strongly correlated with those on overall survival [97]. So, although overall survival did not reach consensus, the COS includes surrogates with which this has a strong correlation. Furthermore, the real-world application of overall survival has been questioned by Prasad et al. Three findings in recent years – survival gains in trials of cancer drugs are marginal, trials of cancer drugs are conducted in unrepresentative populations, and real-world outcomes data find no benefits or diminished benefits of cancer drugs – have coalesced to yield the conclusion that even overall survival in clinical trials in oncology may be a surrogate endpoint [294].

Unlike, overall survival, disease-specific survival benefit does not decrease with age and co-morbidities due to competing risks [294]. Disease-specific survival did reach consensus and some argue that this is a truer reflection of the effects of a treatment than overall survival which reflects all-cause mortality [295]. There is little research regarding the relative benefits of measuring disease-specific survival versus overall survival in OPSCC, and this will need to be investigated in a systematic way in the validation of the COS.

Death related to treatment, which is a grade 5 acute toxicity also reached consensus for inclusion in the COS, yet other acute toxicities did not. The interviews suggested that the long-term adverse effects of treatment are more important to patients and carers than acute effects. This was supported by the Delphi; only 57.9% of patients and carers in panel two and 54.5% of those in panel three ranked acute adverse effects as critically important. Measures of the adverse effects of treatment are a requirement of clinical trials however and acute toxicities were consistently measured in the RCTs identified in the systematic review.

A common criticism of clinical trials in OPSCC is that follow-up periods to assess late adverse effects of treatment are too short, often no more than two years [296]. The qualitative work undertaken here shows that late effects are important to patients and carers and of greater priority than acute effects. Furthermore a growing body of evidence on the late effects of radiotherapy, particularly related to swallowing outcomes necessitates close scrutiny of late sequelae, especially in the HPV-positive cohort of patients who will likely live for longer with late effects. Late radiation related swallowing dysfunction is increasingly observed in patients who are more than five years from completion of radiation treatment, and particularly concerning is the fact that these problems are more common in patients receiving IMRT, a type of radiotherapy thought to reduce xerostomia, another troublesome late effect of radiotherapy [63, 64, 297, 298]. Xerostomia was a common complaint of patients and carers in the qualitative interviews, and the wider literature shows that this is a common patient concern [290]. Yet, the published literature suggests that adverse swallowing outcomes have a more pronounced effect on HR-QOL than mouth dryness [240, 299-301] and, in the Delphi, swallowing was prioritised over mouth dryness. The two outcomes aren't independent however, and mouth dryness contributes substantially to swallowing difficulties in patients treated with radiotherapy for OPSCC. Mouth dryness may be a surrogate for dysphagia.

HR-QOL should be measured in clinical trials in oncology, and this outcome reached consensus in the Delphi. Despite recommendations by the WHO that HR-QOL this should be measured in clinical trials in oncology in 1981, this was only reported in 7 trials in the systematic review, all published after 2006 [239]. There is a strong correlation between HR-QOL and functioning which is why changes in HR-QOL are more pronounced in SCCHN than many other cancers [240]. HR-QOL is an important outcome, and the interviews strongly suggested that this would be an important differentiator for patients and carers when choosing between treatments. HR-QOL is largely measured using questionnaires. There are HR-QOL questionnaires for cancer generally and specifically for SCCHN with construct validity, however no one instrument is ideal for all purposes. When selecting a disease-specific HR-QOL instrument for SCCHN patients, careful consideration must be given to disease subsite, treatment, timing of assessment, clinical setting, study purpose and the research question [302].

The requirement for interventions for the management of treatment-related morbidity reached consensus for inclusion in the COS. This is an outcome domain that arose from the patient and carer interviews. Many described a desire to be cured and free from long-term sequelae of treatment without a requirement for procedures like oesophageal dilatations for dysphagia or further surgery. Several patients described a desire for treatments that were as minimally invasive as possible. When this outcome was presented in the questionnaire it was given with examples of further interventions that were directly taken from the interviews namely the need for further surgery for complications and oesophageal dilatation. Outcomes that are important to patients should not be excluded on the basis that they don't have established ways of measurement. Careful consideration will need to be given as to how this is measured in a systematic and repeatable way in the validation process for the COS.

5.5 Critical evaluation of the research

The systematic review met its stated objective of identifying a comprehensive list of outcomes reported in OPSCC RCTs. This includes clinical and patient-reported outcomes. It has identified inconsistencies in the selection, definition and reporting of outcomes in SCCHN and OPSCC clinical trials which are a barrier to the synthesis of trial data. The search strategy to identify outcomes was rather unfocused and retrieved a large number of citations. Whilst initially, this inclusiveness was seen as a strength of the study, reviewing and sorting such a large number of citations was labour intensive, technically challenging and time consuming. Whilst checks were made, it is possible that this led to the inadvertent exclusion of eligible studies, although it is unlikely that important outcomes were missed.

This review is limited to phase III RCTs. In identifying outcomes of importance other COS developers have also included non-randomised prospective trials, reports of PROMs and qualitative studies [303]. In the design phase of this study we made the decision that the review would be limited to phase III RCTs for the reasons discussed in the introduction. This did limit our review findings to trials of non-surgical interventions - no surgery only trials were identified. The challenges of randomized trials in surgery are well recognized [304], and by only including RCTs we have essentially excluded studies of surgery only interventions and therefore we may be missing outcomes that are important to surgical trials and patients having surgical treatments. This was somewhat compensated for by having a significant proportion of surgically treated patients in our qualitative interviews. None of these had open surgery, however this is rarely a first-line treatment for patients with locally advanced disease in current practice. Although qualitative methods were a key part of the work in this thesis, there is an abundance of HR-QOL literature in SCCHN and including this literature, along with non-randomised and qualitative studies would have increased the number and variety of possible

outcomes to be carried forward to the Delphi study. I don't think any major outcomes were missing however; healthcare professionals and patients and carers suggested few additional outcomes in round one of the Delphi.

The semi-structured interview worked well to identify outcomes of importance, but also to understand why these are important. It allowed me to direct participants back towards discussion about outcomes, when, in discussing very emotive issues some strayed away from discussion around outcomes. The semi-structured approach allowed me to probe some topics further and to ask patients what the most important outcomes were. As a method of data collection, it was rather cathartic for some patients and carers, and several commented that reflecting on their experiences and discussing them had been a really positive experience for them. Some patients also said it was nice that someone was showing an interest in outcomes, because they felt very little concern was given to toxicities, function and their impact on HRQOL. Patients and carers said that by contrast to questionnaires, which they felt were only serving the purpose of the person collecting the data, a face to face interview acknowledged their struggles and was beneficial to them too.

Some patients didn't acknowledge my position as a healthcare professional, however some did and used the interview as an opportunity to address clinical concerns or unanswered questions. They seemed to see me as a go-between though, there was less formality than in their encounters with clinicians who they felt had little time to answer questions, and I was in their home, so the playing field was more level. Although I was seen as someone with knowledge, I don't believe I was seen as a figure of authority.

Initial content analysis allowed me to identify the outcomes and language used to describe them in an expedient manner, to develop my comprehensive outcomes list. Subsequent analysis was more interpretive. As a clinician, in analysing the transcripts to identify outcomes, I will have identified outcomes known to me,

those I recognise through my own experience and knowledge. It is possible that I may have missed outcomes that I didn't recognise, or that don't currently have a means of measurement.

All patients and carers were Caucasian. We attempted to recruit non-Caucasian patients however none were available in the interview timeframe in the UK, which reflects the patient demographic. In the US, only Caucasian patients responded to invitation to participate. Therefore, whilst the COS is broadly generalizable to Caucasian patients in the UK and US, it may not have cross-cultural generalizability. The greatest concern to most patients, aside from survival was of the impact of treatment on eating and drinking. This was more of a concern to patients in whom socialising around food was a priority; in other cultures this may well be even more valued. Additionally, the effects of treatment on aesthetics are likely to have varying levels of cultural significance, which we haven't been able to assess for in this study.

Clinical and demographic data was available for all interviewees, however this was collected less reliably in the Delphi recruitment. This hindered comparisons of voting based on these characteristics, and in randomisation to panels, because these characteristics weren't considered, it is possible that voting was influenced by factors other than panel allocation.

Many participants had difficulty identifying a 'core set' of important outcomes because, as one patient in the Delphi survey commented:

"I wanted to mark nearly everything as critical but realised this defeats the object. At some point over the last 5 years though everything has been critical to me personally."

Whilst many patients and carers understood the need to prioritise some outcomes over others, several found this impossible to do, ranking all the outcomes of critical importance. In this case, not for expedience, but because of a genuine feeling that the outcomes described had all been core, at one point or another. I did not see this as a limitation of the study, rather it points to the significant challenges of selecting core outcomes in conditions with high levels of morbidity. Like in other studies of cancer – survival is the most important outcome - however there was a large 'grey area'; only two out of 56 outcomes in the second round were deemed unimportant by a consensus majority, the rest were either important, or of critical importance.

Attrition was relatively high, with a third of participants dropping out between rounds one and two. The loss of US clinician opinion may have compromised the applicability of the COS to US trials, however given that they did not have minority opinions in the first round of the survey, and that the remaining US participant did not have diverse opinions in the second round, it seems unlikely. Attrition was lowest amongst patient and carer participants who had been involved in the qualitative interviews; this is likely to be because they were more invested in the study. I am certain they felt that their views were genuinely valued because of their involvement throughout the different stages of the COS development process. Published Delphi studies to develop COS report variable levels of attrition between the rounds [117], however, like in this study it seems that attrition is lower with a more targeted recruitment strategy. Bennett et al. observed 0% attrition in their small Delphi study (fewer than 10 participants) and their recruitment strategy was a targeted approach to known experts [198], whereas Smith et al. [204] observed higher attrition rates (17%) from 12 participants from inviting trial authors from the relevant academic literature. A larger study for oesophageal cancer surgery which recruited 126 surgeons and nurses identified through a meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, and by personal knowledge of surgeons, and 185 patients recruited from three clinical centres had attrition rates between rounds 1 and 2 of 15% for professionals and

17% for patients. In a similarly sized study by McNair et al. attrition rates for clinicians were 20% and only 10% for patients [178]. Minimising attrition between the rounds of a Delphi study is important to ensure that minority views are not discounted and that the final consensus represents all stakeholder groups [251]. Although our attrition rate was higher than the other studies quoted, we were able to maintain proportionate representation from the stakeholder groups because we anticipated higher attrition amongst clinicians and therefore invited more to participate in the first round.

To compare and contrast all research in a topic area, a COS must be applicable and adopted internationally. With this in mind, we set out to recruit patient and carer interviewees, and patient, carer and clinician stakeholders in the Delphi from the UK and the US. As discussed, attrition was high amongst US clinicians. Whilst they did not have minority views, it is difficult to predict how they were likely to have voted in round two having seen the feedback from other participants. There was however good participation from US patients in both rounds. We did not extend our recruitment to the rest of Europe, Asia or Australasia however and it is possible that we missed outcomes of importance or of cultural significance.

A further challenge was ensuring that participants engaged in the Delphi process. There were several patient, carer and clinician participants who stated that their beliefs and answers simply hadn't changed between rounds. When feeding back in the second round we showed participants how they had voted on a given outcome in the previous round. Had we not provided this I think participants would have given more time to consider how they ranked outcomes and I think there would have been greater variability in voting. Out of expedience, I think some participants selected the same rankings as they had done previously.

Consistent high ranking could mean participants perceived all of the outcomes to be of critical importance, however there is a risk that participants don't understand

the premise of the consensus exercise – identifying 'core' outcomes. I would argue that the involvement of a smaller number of invested stakeholders is more valuable than the involvement of a greater number of uninvested stakeholders. Invested stakeholders are more likely to remain in the study, understand its purpose and therefore contribute meaningfully to the consensus process. A face to face consensus meeting might make meaningful contribution more likely and would allow for discussion; disengagement could be a product of the online format of the survey.

5.6 Conceptual issues

5.6.1 Integrating healthcare professional and patient and carer views

In this Delphi study, participants were randomised to panels. Only outcomes reaching consensus in every panel were carried forward to the COS. On the one hand, we felt that this would represent the outcomes with the very strongest consensus, however a risk of this type of analysis is that we could have ended up with a very small number of outcomes in the COS should participants have had very disparate views. It would also have been possible to combine all the scores for outcomes and carry forward those reaching cut off, irrespective of whether they reached consensus within individual panels (thus changing the denominator) or to have included all outcomes reaching consensus across the three panels. These methods don't account for stakeholder groups however and the final COS could end up being influenced by a particular stakeholder group if they are more numerous or scores are weighted. Further this could hide those with disparate views. In this study all stakeholder views were given equal weighting in the Delphi analysis, other COS studies have weighted their analysis when a particular stakeholder group's opinion is felt to be more valuable [117]. This is problematic as it is difficult to ascertain what weightings should be given and there is no current guidance on this.

The work by Macefield et al. [287] described in chapter four, that influenced our decision to randomise patients to panels has subsequently been published alongside a review of this methodology by Brookes et al. [289]. This research expanded on the work done by Macefield et al. showing that in three different studies, the randomisation of panel feedback influenced the way participants voted and ultimately the items retained at the end of the Delphi process. The level of agreement between stakeholder groups depends on the feedback presented, even when initial agreement between stakeholders is high. Brookes et al. concluded that all participants in a Delphi should see how individual stakeholder groups have voted, as this may improve agreement between the stakeholder groups by enabling reflection on others' views [289].

In this Delphi study, the variability in voting between rounds suggests that patients and carers were influenced by clinicians but that clinicians weren't influenced by patients and carers. This contrasts with the work undertaken by Macefield et al. which showed that clinicians were more influenced by patients and carers [287]. These findings are potentially at odds with the purpose of the Delphi, which is meant to take away the influence of individuals or groups perceived to have greater authority [251]. It does however also show the value of the consensus exercise; people changed the way they voted in response to others. It could be argued that patients and carers were influenced by factors other than the way clinicians voted. More research is required to establish the factors that influences participants' voting in Delphi studies.

5.6.2 Problems with consensus process

In the development of COS, there is little evidence on the relative advantages and disadvantages of the various consensus methods. As discussed in the introduction to this thesis, expert panel meetings, sometimes using nominal group techniques,

and Delphi studies are the methods used in previous COS studies. These have been used to both elicit opinions and develop consensus [152]. The ability of the method to achieve true consensus amongst a diverse range of stakeholders with methodological rigour is the most important consideration. However, one must also bear in mind factors such as practicality and cost. When designing this study, we therefore considered both consensus methods.

The nominal group technique is a highly-structured face-to-face meeting of 5-9 stakeholders which lasts around 2 hours [182]. Initially there is silent generation of ideas in response to a number of questions. Participants are then invited to share their ideas using a 'round robin' technique until all ideas have been presented. Discussion is discouraged until all ideas have been recorded so that each participant has the opportunity to share their opinion prior to it being modified or rejected by the group. Once all responses are listed, group discussion can ensue to clarify ideas. Finally, participants are asked to prioritise their ideas about each question discussed.

The Delphi technique comprises sequential questionnaires answered anonymously by a panel of participants with relevant expertise. After each questionnaire, the group response is fed back to participants who are asked to reflect on their voting in light of how other participants have voted to move towards group consensus. There must be at least two rounds in a Delphi study to allow reflection on the previous rounds scores. There may also be a 'blank paper' round to elicit opinion prior to scoring items.

Over NGT, one of the advantages of the Delphi method is that it is anonymous. Participants do not meet face to face and there is less chance of more vocal or authoritative figures dominating the discussion or influencing others' voting. This was particularly important in this COS study because we wished to invite patients, carers and healthcare professionals. Perceived imbalances of power amongst such

stakeholders are possible, if not likely, and anonymity went some way to reducing the influence of figures with more perceived authority i.e. healthcare professionals. In one of the panels in our study, feedback from all stakeholder groups was provided, allowing the participants in this panel to reflect on how patients, carers and healthcare professionals had voted. This approach is now recommended by Brookes et al. as it allows for greater consensus between stakeholder groups, however our analysis suggested that patients and carers may have been influenced by healthcare professional's voting because they were more likely to change their voting in response to feedback. This isn't necessarily a methodological flaw, the purpose of the Delphi is for people to change their voting in response to that of others, the limit to which we can reduce the impact of figures of authority in this study is limited however by providing this type of feedback. Some COS studies are currently investigating the reasons for people changing their voting within a Delphi and this will hopefully shed light on the significance of this effect [195, 305].

A further advantage of the Delphi study is that participation can be done remotely using postal or online surveys, and therefore location is of no barrier to participation, which means a more diverse and numerous group of individuals can participate. COS should apply to as wide a geographical audience as possible and so greater geographical diversity of participants is preferential. The Delphi technique has therefore become the most popular method for reaching consensus in COS studies [117].

5.7 Application of the COS

It is likely that the COS is transferrable to other SCCHN subsites, and given that OPSCC is usually studied as part of larger SCCHN clinical trial, for it to be implemented this would have to be accepted, however it must be borne in mind by trialists that a COS represents the minimum that should be reported, and, when used in other subsites additional outcomes may need to be measured. It is likely

that further COS will be developed for other sub-sites, however rather than starting from the beginning it may be that the relevance of the OPSCC COS to other sub-sites could be evaluated by stakeholder working groups for different sub-sites and adapted as deemed necessary. None of the outcomes in the COS are specific to OPSCC, however outcomes that are likely to be important to other head and neck sub-sites are missing; there are no voice outcomes which are likely to be important to clinical trials of interventions for laryngeal cancer.

The COS was designed with late phase clinical trials in OPSCC in mind, however COS in other clinical areas have been applied to other effectiveness studies, research and audit [178], and we would advocate this use. Minimally invasive surgical techniques are increasingly used in the management of patients with OPSCC, yet there are substantial barriers to conducting randomized trials because of the complexity of surgical interventions [306], and no head to head trial comparing surgical and non-surgical interventions has been conducted in SCCHN or OPSCC. As the complexity of surgical trials has been acknowledged [307, 308], research to define the elements of surgical interventions has been conducted with the purpose of increasing the homogeneity of interventions, allowing for robust comparisons of outcomes in RCTs [306]. It is hoped that such research will be conducted for surgical interventions in OPSCC as this is likely to increase the acceptability of surgical interventions to researchers and go some way to reduce the criticisms levelled at the heterogeneous delivery of interventions within RCTs in surgery [309].

Chapter 6
Conclusions and future work

6.1 Main conclusions

Survival remains the most important outcome of treatment to healthcare professionals, patients and carers irrespective of age, disease stage or HPV status. Of the eight outcomes that reached consensus in the Delphi, five of these related to disease control and survival, namely local control, regional control, distant metastatic control, disease-specific survival and death related to treatment. Late toxicities and functional outcomes are important, and were described at length in the interviews, however dysphagia was the only functional outcome to make the COS. Health-related quality of life also reached consensus, however this was more strongly favoured amongst healthcare professionals than patients and carers. In contrast to the significant outcomes heterogeneity identified in the systematic review, there is strong consensus amongst patients, carers and healthcare professionals regarding the outcomes for inclusion in the COS.

This study gathered consensus opinion from major stakeholders regarding the outcomes that should be included in a COS for OPSCC. It is the first study, to my knowledge, which has sought patient opinion regarding outcome selection in clinical trials in OPSCC. The qualitative study described in chapter three, reinforces the existing literature, demonstrating that the adverse effects of treatment for OPSCC are severe, and in many cases, persistent. The implications of these effects are different for patients depending on their age, interests, social circumstances and commitments. The advent of HPV driven OPSCC has seen a change in the 'typical' head and neck cancer patient, and whilst many studies have set out to investigate treatment de-escalation strategies, to reduce the incidence and severity of long-term treatment related morbidity, the qualitative work in this thesis

suggests that those with young children or caring commitments would accept no reduction in survival, for functional gains.

Patients, carers and clinicians were consistent in prioritising survival outcomes. Whilst this is not unexpected, the interviews conducted as part of this study suggested that outcomes such as mouth dryness and fatigue were very important issues for patients both in the acute and long term, yet neither reached consensus for inclusion. Further research is required to interpret the differences in what people say in interviews, compared with how they vote in Delphi studies in COS research.

Mixed methods approaches are useful in core outcome set development for ensuring that outcomes important to all stakeholder groups are considered for inclusion in the COS. The final COS included outcomes extracted from both the systematic review of the literature described in chapter two and the qualitative interviews described in chapter three. Consensus methods are important; the outcomes included in the COS were not the outcomes most commonly measured in the trials included in the review, those spoken about at greatest length in the interviews, or those prioritised by patients and carers in the interviews when asked to rank outcomes. Consensus was strong in this study however, regarding the outcomes of greatest importance, and there were no substantial changes in consensus outcomes between rounds. Without consensus methods, very different conclusions would have been reached regarding the outcomes deemed important to health-care professionals (those measured in trials) and those important to patients and carers (the outcomes discussed during the interviews).

In the Delphi study I took the approach of presenting more precise outcomes rather than outcome ‘domains’ which have been used in other studies. I felt this approach would lessen ambiguity in the interpretation of the outcomes by participants, but also in interpretation of the final published COS by those using it. The next crucial

stage in developing the COS, is in identifying *how* the included outcomes should best be measured. Outcome domains are outcome composites with multiple events per domain that could be measured; this will make the process of identifying best measurement methods more complex and challenging, and is likely to lead to delays in implementation of the COS. We hope that the approach we have taken is still inclusive enough and will allow for efficient dissemination and implementation of the COS.

The COS has benefited from the involvement of patients, carers and clinicians in its development. It is clear from undertaking this exercise that many possible outcomes of treatment could be measured, that different outcomes are prioritised by different individuals but that ultimately there are outcomes of key importance, upon which there was strong consensus.

6.2 Future work

6.2.1 Refining the COS

Work will be ongoing to establish how the included outcomes should be measured, whether this be an objective measure or a subjective measure such as a PROM, and the validity of these instruments will need to be assessed. As well as establishing how the outcomes are measured, definitions, including the events that would be measured need to be clarified, whilst ensuring fidelity to the COS as voted for by participants.

We will be in consultation with COSMIN regarding this, following guidance set out in a joint initiative between COSMIN and COMET on the selection of outcome measurement instruments for COS [310]. This will involve 1) Consideration of the construct to be measured and the target population 2) A systematic review to identify all existing outcome measurement instruments (OMIs) 3) Quality

assessment of OMIs (to evaluate measurement properties and feasibility aspects) 4) Consensus procedures to agree on the OMIs for each outcome in the COS, performed among all relevant stakeholders, including patients.

An important part of this work will be in establishing how the 'need for further interventions as a result of treatment' outcome will be defined and measured; what events will constitute the outcome and how will these be collected in a systematic and repeatable way between trials. Heterogeneous measurement, like heterogeneous outcomes would impede synthesis of such outcomes, and it is possible that a measurement instrument may need to be developed for assessing such events.

Since the induction of this research, a general symptom COS for use in adult cancer treatment trials has been published [311]. We will need to review this and consider how it sits alongside the COS we have developed. The qualitative interview transcripts, and Delphi voting will be useful in assessing the applicability of this COS to clinical trials in OPSCC. Furthermore, in the interim other research groups have made recommendations about OMIs in SCCHN which will have relevance in OPSCC and will be considered as part of the process described above [190].

6.2.2 Validating the COS

The OPSCC COS was developed with healthcare professionals, patients and carers from the UK and US. Further work will be required to establish whether the COS is applicable across international settings. As we work towards refining study populations for OPSCC clinical trials, the need for multi-centre and international trials to recruit adequate numbers will become greater. Therefore, it is of the utmost importance that we establish international applicability of the COS. Furthermore, refinement of study populations means that we will rely more on the

synthesis of data from individual trials. This work is therefore necessary if the COS is to have the intended benefit of harmonising cross-trial outcomes measurement thus facilitating data synthesis.

Expert panels and conference workshops have been used to achieve international consensus by the OMERACT initiative [145], however this was in the design stage of the core set, rather than in assessing its applicability to different international settings. This is however likely to be a useful process for firstly publicising the COS, and secondly opening discussions about whether this has international or cross-cultural validity.

Periodic review of the COS will be necessary to ensure that the included outcomes remain important to stakeholders and relevant to contemporary clinical practice and the changing patient demographic. New outcomes may need to be added and there will need to be a process for considering new outcomes in the context of the scope of the COS. As part of this process, uptake of the COS and barriers to its implementation in relevant trials will need to be assessed and addressed. A process for periodic review of the contents of the COS will need to be delivered.

6.2.3 Uptake of the COS

The protocol for the COS was published and was highly accessed at the time of publication [74]. It has been accessed 3568 times and cited in 20 publications. It has been cited 20 times but only, so far in other COS projects, not related to SCCHN or OPSCC. I have, however, had several enquiries about the COS showing that SCCHN researchers are interested in using this.

The COS development process has also been presented at a number of national meetings, and awareness of the OPSCC COS has grown with increasing awareness of COSs in general. Upon publication, the COS will also be presented at large,

international meetings such as National Cancer Research Institute (NCRI) cancer conference.

COS are under development in other areas of Otorhinolaryngology-Head and Neck Surgery (ORL-HNS), which will hopefully increase awareness of COS amongst head and neck cancer clinicians and researchers and drive trialists to search for COSs when designing OPSCC trials.

This COS is intended for submission to and publication in an open access journal with a large readership to ensure wider publicity and invite feedback. The first COS was published, for rheumatoid arthritis, in 1994. The introduction of regulatory guidance recommending use of the COS by the Food and Drug Administration (FDA) in 1996 and the European Medicines Agency (EMA) in 1998 are thought to have contributed to trials measuring these outcomes. In addition to raising awareness of the COS with regulatory agencies we will need to engage with organisations such as the European Organisation for Research and Treatment of Cancer (EORTC), the United States National Cancer Institute (NCI) and the Radiation Therapy Oncology Group (RTOG) to validate the COS more widely and ensure its' implementation in major OPSCC clinical trials.

The promotion of COS by the COMET initiative [175] and references to COS in guidelines for trialists [312], by funders [313] and from regulatory authorities [314] are expected to accelerate COS uptake in the future. Furthermore, engagement with journal editors, funders, Cochrane Review Groups, clinical guidelines developers and trial registries will increase COS uptake by incentivising trialists to use them [315].

Evaluation of COS uptake is crucial to avoid core outcome sets being developed but never used, thereby contributing to research waste [316]. Uptake of the COS will be assessed by consultation of trial registries. In a recent review by Kirkham et

al. [315] this was shown to provide a reasonable estimate of the uptake of COS and is a more efficient and up-to-date approach than examining the outcomes in published trial reports or by citation analysis [317].

Barriers to implementation of the COS should be anticipated and addressed. One potential barrier is of difficulty finding the COS. It will be made clear in the title and abstract of the publication that this is a COS for OPSCC, as by the COS-STAR recommendations [318]; it will be listed in the COMET database and published, as described above, in an open access journal. COS are indexed inconsistently in literature databases; research is required to establish best practice for indexing and labelling such research. A further barrier to implementation could be that the outcomes are difficult or expensive to measure, making it unfeasible to use the COS in certain settings. This will be reflected in the uptake of the COS and a further systematic review to identify trials not using the COS with exploration of the reasons for not doing so may be helpful.

6.2.4 Optimising patient involvement in COS

Patients and carers were crucial in developing the COS, and future co-working with patients and carers will be essential as the COS adapts over time. Nearly 90% of ongoing COS studies registered in the COMET database involve patient and public involvement (PPI) stakeholders, and COMET have launched the People and Patient Participation, Involvement and Engagement (PoPPIE) working group to lead and oversee the public participation, involvement and engagement work of the COMET initiative [157]. We will use their resources in planning public involvement in future work on our COS.

6.2.5 Intended publications arising from the work in this thesis

The systematic review described in chapter two is currently being updated and will submitted for publication in a head and neck journal. The series of qualitative interviews in chapter three and the Delphi study described in chapter four will be submitted as a combined paper to a general open access journal, this will outline the process of identifying the comprehensive outcomes list, the Delphi study and the final COS. A further paper exploring other issues arising from the qualitative interviews is currently under consideration. Further publications will arise from the research to refine and validate the COS and establish how the outcomes should be measured. A systematic review of PROMs in SCCHN is also under way.

6.2.6 Future methodological research

This methodological research is novel and has highlighted a number of important considerations for future COS developers, including areas for future methodological research.

6.2.6.1 Streamlining the systematic review

We used a Cochrane search strategy and RCT filter to identify outcomes for the comprehensive outcomes list. As discussed, a large number of citations were retrieved, and this is a problem described in other COS studies, especially those searching for other study types. Future methodological research to identify ways to streamline this part of the research process would be useful, along with consideration to the indexing of COS studies in bibliographic databases.

6.2.6.2 Delphi process

The Delphi undertaken as part of this study raised questions about the impact of attrition, factors that contribute to this, ideal participant numbers in Delphi studies, the effect of greater or lesser investment in the study on responses, the effect of panels and how best to analyse the data. Furthermore this study raised questions about patient and carer understanding of the process because they consistently ranked more outcomes highly and had greater difficulty identifying a core of important outcomes. There are ongoing nested methodological studies hoping to answer some of these questions and it is hoped that this study will help to inform some of this literature.

6.2.6.3 Comparing or synthesising different COS

This research has some overlap with the ICF core set for head and neck cancer, and, although the COMET database aims to avoid duplication of COS research it is possible that other COS for OPSCC will be developed. COS for other SCCHN subsites may also be developed. An important consideration for COS developers is how this research can be compared and or synthesised. There is no research that I am aware of that is exploring this currently.

6.3 Final summary

This study has identified eight outcomes to be included in a core outcome set for clinical trials in oropharyngeal cancer using a mixed methods approach, requiring involvement of patients, carers and healthcare professionals in identifying the outcomes and subsequently prioritising these using iterative consensus techniques. The methods used in this study have been effective in reaching strong consensus and I have identified areas for further methodological research. COS are growing in number, and a concerted effort is required amongst those involved in clinical research to make sure that the most appropriate outcomes are measured and included in COS which are consistently applied and reported in clinical trials. The

selection of better outcomes provides more robust evidence for the effectiveness of interventions, this should, in turn, inform clinical practice and clinical guidelines and, ultimately, lead to improvements in patient care.

List of references

1. Pai, S.I. and W.H. Westra, *Molecular Pathology of Head and Neck Cancer: Implications for Diagnosis, Prognosis, and Treatment.* Annual review of pathology, 2009. **4**: p. 49-70.
2. Mehanna, H., O. Olaleye, and L. Licitra, *Oropharyngeal cancer - Is it time to change management according to human papilloma virus status?* Current Opinion in Otolaryngology and Head and Neck Surgery, 2012. **20**(2): p. 120-124+150.
3. Kamangar, F., G.M. Dores, and W.F. Anderson, *Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world.* J Clin Oncol, 2006. **24**(14): p. 2137-50.
4. Poon CS, S.K., *Overview of the diagnosis and staging of head and neck cancer*. UpToDate, ed. F.M. Brockstein BE. UpToDate, Waltham, MA (Accessed on January 25, 2017).
5. Bauman, J.E. and R.L. Ferris, *Integrating novel therapeutic monoclonal antibodies into the management of head and neck cancer.* Cancer, 2014. **120**(5): p. 624-632.
6. Murphy, B.A., et al., *Quality of life research in head and neck cancer: a review of the current state of the science.* Crit Rev Oncol Hematol, 2007. **62**(3): p. 251-67.
7. Lewin, F., et al., *Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck.* Cancer, 1998. **82**(7): p. 1367-1375.
8. Andre, K., et al., *Role of alcohol and tobacco in the aetiology of head and neck cancer: a case-control study in the Doubs region of France.* European Journal of Cancer Part B: Oral Oncology, 1995. **31**(5): p. 301-309.
9. Chen, A.M., et al., *Tobacco Smoking During Radiation Therapy for Head-and-Neck Cancer Is Associated With Unfavorable Outcome.* International Journal of Radiation Oncology • Biology • Physics, 2011. **79**(2): p. 414-419.
10. Sturgis, E.M. and K.K. Ang, *The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms?* Journal of the National Comprehensive Cancer Network, 2011. **9**(6): p. 665-673.
11. Johnson, S., et al., *Socio-economic status and head and neck cancer incidence in Canada: a case-control study.* Oral oncology, 2010. **46**(3): p. 200-203.
12. Johnson, S., J.T. McDonald, and M.J. Corsten, *Socioeconomic factors in head and neck cancer.* Journal of Otolaryngology--Head & Neck Surgery, 2008. **37**(4).
13. Conway, D.I., et al., *Components of socioeconomic risk associated with head and neck cancer: A population-based case–control study in Scotland.* British Journal of Oral and Maxillofacial Surgery. **48**(1): p. 11-17.
14. Gustavsson, P., et al., *Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden.* Occupational and Environmental Medicine, 1998. **55**(6): p. 393-400.
15. Rosenquist, K., *Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden.* Swedish dental journal. Supplement, 2005(179): p. 1-66.
16. De Stefani, E., et al., *Dietary patterns and risk of cancer of the oral cavity and pharynx in Uruguay.* Nutrition and cancer, 2005. **51**(2): p. 132-139.
17. Tavani, A., et al., *Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer.* Oral oncology, 2003. **39**(7): p. 695-700.

18. Toporcov, T.N., J.L.F. Antunes, and M.R. Tavares, *Fat food habitual intake and risk of oral cancer.* Oral oncology, 2004. **40**(9): p. 925-931.
19. Guha, N., et al., *Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies.* American journal of epidemiology, 2007. **166**(10): p. 1159-1173.
20. McDonald, J.T., et al., *The relationship between survival and socio-economic status for head and neck cancer in Canada.* Journal of Otolaryngology-Head & Neck Surgery, 2014. **43**(1): p. 2.
21. Rylands, J., D. Lowe, and S.N. Rogers, *Outcomes by area of residence deprivation in a cohort of oral cancer patients: survival, health-related quality of life, and place of death.* Oral oncology, 2016. **52**: p. 30-36.
22. Auluck, A., et al., *Population-based incidence trends of oropharyngeal and oral cavity cancers by sex among the poorest and underprivileged populations.* BMC cancer, 2014. **14**(1): p. 316.
23. Zandberg, D.P., et al., *Oropharyngeal cancer as a driver of racial outcome disparities in squamous cell carcinoma of the head and neck: 10-year experience at the University of Maryland Greenebaum Cancer Center.* Head & neck, 2016. **38**(4): p. 564-572.
24. Kwok, J., et al., *The impact of health insurance status on the survival of patients with head and neck cancer.* Cancer, 2010. **116**(2): p. 476-485.
25. Aizer, A.A., et al., *Marital Status and Survival in Patients With Cancer.* Journal of Clinical Oncology, 2013. **31**(31): p. 3869-3876.
26. Ayanian, J.Z., et al., *The relation between health insurance coverage and clinical outcomes among women with breast cancer.* New England Journal of Medicine, 1993. **329**(5): p. 326-331.
27. Aizer, A.A., et al., *Multidisciplinary care and pursuit of active surveillance in low-risk prostate cancer.* Journal of Clinical Oncology, 2012. **30**(25): p. 3071-3076.
28. Goldzweig, G., et al., *Psychological distress among male patients and male spouses: what do oncologists need to know?* Annals of Oncology, 2009. **21**(4): p. 877-883.
29. Dronkers, E.A.C., et al., *Noncompliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician.* BMC Cancer, 2015. **15**: p. 515.
30. Pajak, T.F., et al., *Elapsed treatment days—a critical item for radiotherapy quality control review in head and neck trials: RTOG report.* International Journal of Radiation Oncology• Biology• Physics, 1991. **20**(1): p. 13-20.
31. Price, G., et al., *Profile of head and neck cancers in England: incidence, mortality and survival*. 2010, Oxford: Oxford Cancer Intelligence Unit.
32. Chaturvedi, A., et al., *Human papillomavirus (HPV) and rising oropharyngeal cancer incidence and survival in the United States.* Journal of Clinical Oncology, 2011. **1)**.
33. K, R., *Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern sweden*Swed Dent J Suppl, 2005(179): p. 1-66.
34. Chaturvedi, A.K., et al., *Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers.* J Clin Oncol, 2013. **31**.
35. Hong, A., et al., *Rising prevalence of human papillomavirus-related oropharyngeal cancer in Australia over the last 2 decades.* Head Neck, 2016. **38**(5): p. 743-50.
36. Chaturvedi, A.K., et al., *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* Journal of Clinical Oncology, 2011. **29**(32): p. 4294-4301.
37. Schache, A.G., et al., *HPV-related oropharyngeal cancer in the United Kingdom: an evolution in understanding of disease etiology.* Cancer Research, 2016.

38. van Monsjou, H.S., et al., *The epidemiology of head and neck squamous cell carcinoma in The Netherlands during the era of HPV-related oropharyngeal squamous cell carcinoma. Is there really evidence for a change?* Oral Oncology, 2015. **51**(10): p. 901-907.
39. Rietbergen, M.M., et al., *Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm.* International journal of cancer, 2013. **132**(7): p. 1565-1571.
40. Henneman, R., et al., *Incidence changes of human papillomavirus in oropharyngeal squamous cell carcinoma and effects on survival in the Netherlands Cancer Institute, 1980-2009.* Anticancer research, 2015. **35**(7): p. 4015-4022.
41. Melchers, L., et al., *Detection of HPV-associated oropharyngeal tumours in a 16-year cohort: more than meets the eye.* British journal of cancer, 2015. **112**(8): p. 1349.
42. Gillison, M., *HPV and its effect on head and neck cancer prognosis.* Clinical Advances in Hematology and Oncology, 2010. **8**(10): p. 680-682.
43. Ragin, C.C.R. and E. Taioli, *Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis.* International Journal of Cancer, 2007. **121**(8): p. 1813-1820.
44. Fakhry, C., et al., *Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial.* Journal of the National Cancer Institute, 2008. **100**(4): p. 261-269.
45. Ang , K.K., et al., *Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer.* New England Journal of Medicine, 2010. **363**(1): p. 24-35.
46. List, M.A., et al., *How Do Head and Neck Cancer Patients Prioritize Treatment Outcomes Before Initiating Treatment?* Journal of Clinical Oncology, 2000. **18**(4): p. 877.
47. Blanchard, P., et al., *Assessing head and neck cancer patient preferences and expectations: A systematic review.* Oral Oncol, 2016. **62**: p. 44-53.
48. O'Rorke, M.A., et al., *Human papillomavirus related head and neck cancer survival: A systematic review and meta-analysis.* Oral Oncology, 2012. **48**(12): p. 1191-1201.
49. Parsons, J.T., et al., *Squamous cell carcinoma of the oropharynx.* Cancer, 2002. **94**(11): p. 2967-2980.
50. Carter, R., et al., *Perineural spread in squamous cell carcinomas of the head and neck: a clinicopathological study.* Clinical Otolaryngology, 1979. **4**(4): p. 271-281.
51. Feldman, M. and G.H. Fletcher, *Analysis of the parameters relating to failures above the clavicles in patients treated by postoperative irradiation for squamous cell carcinomas of the oral cavity or oropharynx.* International Journal of Radiation Oncology* Biology* Physics, 1982. **8**(1): p. 27-30.
52. Johnson, J.T., et al., *The Extracapsular Spread of Tumors.* Arch Otolaryngol, 1981. **107**: p. 725-729.
53. Looser, K.G., J.P. Shah, and E.W. Strong, *The significance of "positive" margins in surgically resected epidermoid carcinomas.* Head & Neck, 1978. **1**(2): p. 107-111.
54. Shah, J.P., et al., *Carcinoma of the oral cavity: factors affecting treatment failure at the primary site and neck.* The American Journal of Surgery, 1976. **132**(4): p. 504-507.
55. Kramer, S., et al., *Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73–03 of the Radiation Therapy Oncology Group.* Head & Neck, 1987. **10**(1): p. 19-30.
56. Lavaf, A., et al., *Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma.* Cancer, 2008. **112**(3): p. 535-543.

57. Mehanna, H., O. Olaleye, and L. Licitra, *Oropharyngeal cancer – is it time to change management according to human papilloma virus status?* Current Opinion in Otolaryngology & Head and Neck Surgery, 2012. **20**(2): p. 120-124.
58. Rackley, T., et al., *Adjuvant treatment decisions for oropharyngeal cancer – is it time for a change?* Clinical Otolaryngology, 2014. **39**(5): p. 316-321.
59. Pignon, J.P., et al., *Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients.* Radiotherapy and Oncology, 2009. **92**(1): p. 4-14.
60. Dillon, M.T. and K.J. Harrington, *Human papillomavirus–negative pharyngeal cancer.* Journal of Clinical Oncology, 2015. **33**(29): p. 3251-3261.
61. Trotti, A., et al., *Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review.* Radiother Oncol, 2003. **66**(3): p. 253-62.
62. Hutcheson, K.A. and J.S. Lewin, *Functional Outcomes after Chemoradiotherapy of Laryngeal and Pharyngeal Cancers.* Current oncology reports, 2012. **14**(2): p. 158-165.
63. Hutcheson, K.A., et al., *Late dysphagia after radiotherapy-based treatment of head and neck cancer.* Cancer, 2012. **118**(23): p. 5793-9.
64. Hutcheson, K.A., et al., *Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: video case reports.* Head Neck, 2015. **37**(4): p. E56-62.
65. Bernier, J., et al., *Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.* The New England journal of medicine, 2004. **350**(19): p. 1945-1952.
66. Cooper, J.S., et al., *Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.* The New England journal of medicine, 2004. **350**(19): p. 1937-1944.
67. Steiner, W., et al., *Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue.* Archives of Otolaryngology–Head & Neck Surgery, 2003. **129**(1): p. 36-43.
68. Haughey, B.H., et al., *Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: A united states multicenter study.* Head & neck, 2011. **33**(12): p. 1683-1694.
69. de Almeida, J.R., et al., *Oncologic outcomes after transoral robotic surgery : A multi-institutional study.* JAMA Otolaryngology–Head & Neck Surgery, 2015. **141**(12): p. 1043-1051.
70. Ang, K.K., et al. *Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**, 2940-50 DOI: 10.1200/JCO.2013.53.5633.
71. Lauer, M.S. and R.B. D'Agostino Sr, *The randomized registry trial—the next disruptive technology in clinical research.* N Engl J Med, 2013. **369**(17): p. 1579-81.
72. Jernberg, T., et al., *The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART).* Heart, 2010. **96**(20): p. 1617-1621.
73. James, S., S.V. Rao, and C.B. Granger, *Registry-based randomized clinical trials—a new clinical trial paradigm.* Nature Reviews Cardiology, 2015. **12**(5): p. 312.

74. Waters AMI, S.C., Young B, Jones TM, *The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer.* Trials, 2014. **15**(168).
75. Flay, B.R., *Efficacy and effectiveness trials (and other phases of research) in the development of health promotion programs.* Preventive medicine, 1986. **15**(5): p. 451-474.
76. Godwin, M., et al., *Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity.* BMC medical research methodology, 2003. **3**(1): p. 28.
77. NICE, *The guidelines manual 2012.* 2012.
78. Guyatt, G.R., D, *Users' guide to the medical literature: a manual for evidence-based clinical practice.* Amer Medical Assn,, 2002.
79. Akobeng, A., *Understanding randomised controlled trials.* Archives of disease in childhood, 2005. **90**(8): p. 840-844.
80. Moher, D., et al., *CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**.
81. Greenland, S., *Randomization, statistics, and causal inference.* Epidemiology, 1990: p. 421-429.
82. Armitage, P., *The role of randomization in clinical trials.* Statistics in medicine, 1982. **1**(4): p. 345-352.
83. Kleijnen, J., et al., *So what´ s so special about randomisation*, in *Non-random Reflections on Health Services Research: on the 25 Anniversary of Archie Cochrane´ s Effectiveness and Efficiency*. 1997, BMJ Publishing Group Ltd. p. 231-249.
84. Freemantle, N., et al., *Composite outcomes in randomized trials: Greater precision but with greater uncertainty?* JAMA, 2003. **289**(19): p. 2554-2559.
85. administration., D.o.H.a.H.S.F.a.D., *Internation conference on harmonisation; guidance on statistical principles for clinical trials.* Federal Register, 1998. **63**: p. 49583-98.
86. Freemantle, N., *Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic?* BMJ, 2001. **322**(7292): p. 989-991.
87. Smyth, R.M.D., et al., *Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists.* BMJ, 2011. **342**.
88. Godwin, M., et al., *Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity.* BMC Med Res Methodol, 2003. **3**: p. 28.
89. Higgins, J.a.S.G., [Editors], *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011].* 2011.
90. Biomarkers Definitions Working, G., *Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework.* Clinical Pharmacology & Therapeutics, 2001. **69**(3): p. 89-95.
91. Yudkin, J.S., K.J. Lipska, and V.M. Montori, *The idolatry of the surrogate.* BMJ: British Medical Journal (Online), 2011. **343**.
92. Messerli, F.H. and S. Bangalore, *ALTITUDE trial and dual RAS blockade: the alluring but soft science of the surrogate end point.* The American journal of medicine, 2013. **126**(3): p. e1-e3.
93. Fleming, T.R. and D.L. DeMets, *Surrogate end points in clinical trials: are we being misled?* Annals of internal medicine, 1996. **125**(7): p. 605-613.
94. Prasad, V., et al., *The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses.* JAMA internal medicine, 2015. **175**(8): p. 1389-1398.

95. Saad, E.D., A. Katz, and M. Buyse, *Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials.* Journal of clinical oncology, 2010. **28**(11): p. 1958-1962.
96. Davis, C., et al., *Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: Retrospective cohort study of drug approvals 2009-13.* BMJ (Online), 2017. **359**.
97. Michiels, S., et al., *Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data.* The lancet oncology, 2009. **10**(4): p. 341-350.
98. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* American journal of clinical oncology, 1982. **5**(6): p. 649-656.
99. Therasse, P., et al., *New guidelines to evaluate the response to treatment in solid tumors.* Journal of the National Cancer Institute, 2000. **92**(3): p. 205-216.
100. Pignon, J.P., et al., *Chemotherapy added to locoregional treatment for head and squamous-cell carcinoma: three meta-analyses of updated individual data.* Lancet, 2000. **355**.
101. Adelstein, D.J. and M. LeBlanc, *Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer?* Journal of clinical oncology, 2006. **24**(17): p. 2624-2628.
102. McKee, A.E., et al., *The role of the US Food and Drug Administration review process: clinical trial endpoints in oncology.* The oncologist, 2010. **15**(Supplement 1): p. 13-18.
103. Buyse, M., et al., *The validation of surrogate endpoints in meta-analyses of randomized experiments.* Biostatistics, 2000. **1**(1): p. 49-67.
104. Buyse, M., et al., *Biomarkers and surrogate end points—the challenge of statistical validation.* Nature reviews Clinical oncology, 2010. **7**(6): p. 309.
105. Group*, D.o.V.A.L.C.S., *Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer.* New England Journal of Medicine, 1991. **324**(24): p. 1685-1690.
106. Forastiere, A.A., et al., *Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer.* N Engl J Med, 2003. **349**.
107. Forastiere, A., et al., *Long-term results of Intergroup RTOG 91–11: a phase III trial to preserve the larynx—induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy.* Journal of Clinical Oncology, 2006. **24**(18_suppl): p. 5517-5517.
108. Group, R.T.O., *RTOG 1016: phase III trial of radiotherapy plus cetuximab versus chemoradiotherapy in HPV-associated oropharynx cancer*. 2014.
109. Cordoba, G., et al., *Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review.* BMJ, 2010. **341**.
110. Ferreira-González, I., et al., *Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns.* Journal of clinical epidemiology, 2007. **60**(7): p. 651-657.
111. Le Tourneau, C., et al., *Reporting of time-to-event end points and tracking of failures in randomized trials of radiotherapy with or without any concomitant anticancer agent for locally advanced head and neck cancer.* Journal of Clinical Oncology, 2009. **27**(35): p. 5965-5971.
112. administration, U.S.D.o.h.a.h.s.f.a.d., *US Food and Drug Administration: Guidance for Industry: Patient-reported outcome measures: use in medical product development to support labeling claims.* 2009.

113. Calvert, M., et al., *The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice.* Health Qual Life Outcomes, 2013. **11**: p. 184.
114. Willke, R.J., L.B. Burke, and P. Erickson, *Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels.* Control Clin Trials, 2004. **25**(6): p. 535-52.
115. Sanders, C., et al., *Reporting on quality of life in randomised controlled trials: bibliographic study.* BMJ, 1998. **317**(7167): p. 1191.
116. Calvert, M., et al., *Reporting of patient-reported outcomes in randomized trials: The consort pro extension.* JAMA, 2013. **309**(8): p. 814-822.
117. Williamson, P.R., et al., *The COMET handbook: version 1.0.* Trials, 2017. **18**(3): p. 280.
118. Bakas, T., et al., *Systematic review of health-related quality of life models.* Health and quality of life outcomes, 2012. **10**(1): p. 134.
119. WHO, *WHO definition of Health.* 1948.
120. Idzerda, L., et al., *Can we decide which outcomes should be measured in every clinical trial? A scoping review of the existing conceptual frameworks and processes to develop core outcome sets.* J Rheumatol, 2014. **41**(5): p. 986-93.
121. Huber, M., et al., *How should we define health?* BMJ, 2011. **343**.
122. Tschiesner, U., et al., *Developing core sets for patients with head and neck cancer based on the International Classification of Functioning, Disability and Health (ICF).* Eur Arch Otorhinolaryngol, 2007. **264**(10): p. 1215-22.
123. NIH, *Patient-Reported Outcomes Measurement Information System–PROMIS.*
124. Fries, J.F., et al., *Measurement of patient outcome in arthritis.* Arthritis & Rheumatology, 1980. **23**(2): p. 137-145.
125. Wilson, I.B. and P.D. Cleary, *Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes.* Jama, 1995. **273**(1): p. 59-65.
126. Chiarotto, A., et al., *Core outcome domains for clinical trials in non-specific low back pain.* European Spine Journal, 2015. **24**(6): p. 1127-1142.
127. Gliklich, R.E., et al., *A framework for creating standardized outcome measures for patient registries.* Journal of comparative effectiveness research, 2014. **3**(5): p. 473-480.
128. Smith, V., et al., *Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported.* Journal of clinical epidemiology, 2015. **68**(3): p. 237-245.
129. Tovey, D., *Impact of Cochrane Reviews [editorial], The Cochrane Library.; 2010*.
130. Kirkham, J.J., M. Clarke, and P.R. Williamson, *A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis.* BMJ, 2017. **357**.
131. Kirkham, J., et al., *Outcome measures in rheumatoid arthritis randomised trials over the last 50 years.* Trials, 2013. **14**(1): p. 324.
132. Hutton, J. and P.R. Williamson, *Bias in meta-analysis due to outcome variable selection within studies.* Journal of the Royal Statistical Society: Series C (Applied Statistics), 2000. **49**(3): p. 359-370.
133. Kirkham, J.J., et al., *The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews.* BMJ, 2010. **340**.
134. Kirkham, J.J., et al., *The impact of outcome reporting bias on systematic reviews.* BMJ, 2010. **340**: p. c365.
135. Chan, A.-W., et al., *Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research.* Canadian Medical Association Journal, 2004. **171**(7): p. 735-740.

136. Chan, A.-W., et al., *Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles.* Jama, 2004. **291**(20): p. 2457-2465.
137. Dickersin, K., et al., *Publication bias and clinical trials.* Controlled clinical trials, 1987. **8**(4): p. 343-353.
138. Dwan, K., et al., *Systematic review of the empirical evidence of study publication bias and outcome reporting bias.* PLoS ONE, 2008. **3**(8): p. e3081.
139. Dwan, K., et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review.* PLOS ONE, 2013. **8**(7): p. e66844.
140. Song, F., et al., *Dissemination and publication of research findings: an updated review of related biases.* Health Technol Assess, 2010. **14**(8): p. 1-193.
141. Rothstein, H.R., A.J. Sutton, and M. Borenstein, *Publication bias in meta-analysis: Prevention, assessment and adjustments*. 2006: John Wiley & Sons.
142. Dickersin, K. and Y. Min, *NIH clinical trials and publication bias*. 1993.
143. Stern, J.M. and R.J. Simes, *Publication bias: evidence of delayed publication in a cohort study of clinical research projects.* Bmj, 1997. **315**(7109): p. 640-645.
144. WHO, *Constitution of the World Health Organization.* 2006.
145. Tugwell, P., et al., *OMERACT: An international initiative to improve outcome measurement in rheumatology.* Trials, 2007. **8**(1): p. 38.
146. Boers, M., et al., *Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0.* J Clin Epidemiol, 2014. **67**(7): p. 745-53.
147. IMMPACT, *Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.* Accessed March 2018.
148. HOME, *Harmonising Outcome Measures for Eczema.* Accessed 24 March 2018.
149. Tunis, S.R., et al., *Improving the relevance and consistency of outcomes in comparative effectiveness research.* Journal of comparative effectiveness research, 2016. **5**(2): p. 193-205.
150. Gargon, E., et al., *The COMET Initiative database: progress and activities from 2011 to 2013.* Trials, 2014. **15**(1): p. 279.
151. Gargon, E., et al., *The COMET initiative database: progress and activities update (2014).* Trials, 2015. **16**(1): p. 515.
152. Williamson, P.R., et al., *Developing core outcome sets for clinical trials: issues to consider.* Trials, 2012. **13**(1): p. 132.
153. Products, T.E.A.f.t.E.o.M., *Guideline on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis.* 2003.
154. FDA, U.D.o.H.H.S., *1999.*
155. Khan, K.S. and R. Romero, *The CROWN Initiative: journal editors invite researchers to develop core outcomes in women’s health.* American Journal of Obstetrics & Gynecology. **211**(6): p. 575-576.
156. de Wit, M., et al., *Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences.* BMJ Open, 2013. **3**(5).
157. http://www.comet-initiative.org/ppi/poppie.
158. Begg, C., et al., *Improving the quality of reporting of randomized controlled trials: the CONSORT statement.* Jama, 1996. **276**(8): p. 637-639.
159. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMC medicine, 2010. **8**(1): p. 18.

160. Moher, D., et al., *The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials*. 2001, Elsevier.
161. Turner, L., et al., *Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane reviewa.* Systematic Reviews, 2012. **1**(1): p. 60.
162. Gargon, E., et al., *Choosing important health outcomes for comparative effectiveness research: a systematic review.* PloS one, 2014. **9**(6): p. e99111.
163. Hirsch, B.R., et al., *Characteristics of oncology clinical trials: insights from a systematic analysis of ClinicalTrials.gov.* JAMA Intern Med, 2013. **173**(11): p. 972-9.
164. Kirkham, J.J., et al., *Can a core outcome set improve the quality of systematic reviews?–a survey of the Co-ordinating Editors of Cochrane Review Groups.* Trials, 2013. **14**(1): p. 21.
165. Blencowe, N.S., et al., *Standards of outcome reporting in surgical oncology: a case study in esophageal cancer.* Annals of surgical oncology, 2012. **19**(13): p. 4012-4018.
166. Thornley, B. and C. Adams, *Content and quality of 2000 controlled trials in schizophrenia over 50 years.* Bmj, 1998. **317**(7167): p. 1181-1184.
167. Chalmers, I. and P. Glasziou, *Avoidable waste in the production and reporting of research evidence.* Obstetrics & Gynecology, 2009. **114**(6): p. 1341-1345.
168. Trotti, A., et al., *Patient-Reported Outcomes and the Evolution of Adverse Event Reporting in Oncology.* Journal of Clinical Oncology, 2007. **25**(32): p. 5121-5127.
169. Furness, S., A.-M. Glenny, et al, *Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy.* Cochrane Database of Systematic Reviews, 2011.
170. Glenny, A.-M., S. Furness, et al, *Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy.* Cochrane Database of Systematic Reviews 2011.
171. Bessell A, G.A., Furness S, Clarkson JE, Oliver R, Conway DI, Macluskey M, Pavitt S, Sloan P, Worthington HV, *Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment.* Cochrane Database of Systematic Reviews, 2011.
172. Machtay, M., et al., *Factors Associated With Severe Late Toxicity After Concurrent Chemoradiation for Locally Advanced Head and Neck Cancer: An RTOG Analysis.* Journal of Clinical Oncology, 2008. **26**(21): p. 3582-3589.
173. Howard, J., et al., *Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma.* Cochrane Database of Systematic Reviews, 2016(12).
174. Blanchard, P., et al., *Assessing head and neck cancer patient preferences and expectations: A systematic review.* Oral Oncology. **62**: p. 44-53.
175. initiative, C.
176. Sinha, I.P., P.R. Williamson, and R.L. Smyth, *Outcomes in Clinical Trials of Inhaled Corticosteroids for Children with Asthma Are Narrowly Focussed on Short Term Disease Activity.* PLoS ONE, 2009. **4**(7): p. e6276.
177. Harman, N.L., et al., *The Importance of Integration of Stakeholder Views in Core Outcome Set Development: Otitis Media with Effusion in Children with Cleft Palate.* PLOS ONE, 2015. **10**(6): p. e0129514.
178. McNair, A.G., et al., *Core Outcomes for Colorectal Cancer Surgery: A Consensus Study.* PLoS Med, 2016. **13**(8): p. e1002071.
179. http://www.cosmin.nl/.
180. Mokkink, L.B., et al., *The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes.* Journal of clinical epidemiology, 2010. **63**(7): p. 737-745.

181. INVOLVE, *What is public involvement in research?*
182. Potter, M., S. Gordon, and P. Hamer, *The nominal group technique: a useful consensus methodology in physiotherapy research.* New Zealand Journal of Physiotherapy, 2004. **32**: p. 126-130.
183. Harvey, N. and C.A. Holmes, *Nominal group technique: an effective method for obtaining group consensus.* International journal of nursing practice, 2012. **18**(2): p. 188-194.
184. Basch, C.E., *Focus group interview: an underutilized research technique for improving theory and practice in health education.* Health education quarterly, 1987. **14**(4): p. 411-448.
185. Krueger, R.A., *Focus Groups Second Edition: A Practical Guide of Applied Researchers*. 1994, Thousand Oaks, California: SAGE Publications.
186. Dalkey, N. and O. Helmer, *An experimental application of the Delphi method to the use of experts.* Management science, 1963. **9**(3): p. 458-467.
187. Waters, A.M., et al., *The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer.* Trials, 2014. **15**: p. 168.
188. Gorst, S.L., et al., *Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps.* PloS one, 2016. **11**(12): p. e0168403.
189. Johnson, R.B., A.J. Onwuegbuzie, and L.A. Turner, *Toward a Definition of Mixed Methods Research.* Journal of Mixed Methods Research, 2007. **1**(2): p. 112-133.
190. Ringash, J., et al., *Outcomes toolbox for head and neck cancer research.* Head & neck, 2015. **37**(3): p. 425-439.
191. Tschiesner, U., et al., *Content comparison of quality of life questionnaires used in head and neck cancer based on the international classification of functioning, disability and health: a systematic review.* Eur Arch Otorhinolaryngol, 2008. **265**(6): p. 627-37.
192. Tschiesner, U., et al., *Development of ICF core sets for head and neck cancer.* Head & Neck, 2010. **32**(2): p. 210-220.
193. Tschiesner, U., et al., *Evaluating sequelae after head and neck cancer from the patient perspective with the help of the International Classification of Functioning, Disability and Health.* Eur Arch Otorhinolaryngol, 2009. **266**(3): p. 425-36.
194. Keeley, T., et al., *The use of qualitative methods to inform Delphi surveys in core outcome set development.* Trials, 2016. **17**(1): p. 230.
195. MacLennan, S., et al., *A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey.* Trials, 2015. **16**(1): p. 76.
196. Gargon, E., P.R. Williamson, and B. Young, *Improving core outcome set development: qualitative interviews with developers provided pointers to inform guidance.* Journal of clinical epidemiology, 2017. **86**: p. 140-152.
197. Chalmers, K., et al., *What is the effect of patient-reported outcome (PRO) item order on prioritisation of PROs in the development of a core outcome set?* Trials, 2015. **16**(2): p. O73.
198. Bennett, W.L., et al., *High priority research needs for gestational diabetes mellitus.* Journal of Women's Health, 2012. **21**(9): p. 925-932.
199. Schmitt, J., et al., *Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process.* Journal of Investigative Dermatology, 2011. **131**(3): p. 623-630.
200. Potter, S., et al., *Development of a core outcome set for research and audit studies in reconstructive breast surgery.* British Journal of Surgery, 2015. **102**(11): p. 1360-1371.

201. Blazeby, J., et al., *Core information set for oesophageal cancer surgery.* BJS, 2015. **102**(8): p. 936-943.
202. Kloppenburg, M., et al., *Report from the OMERACT Hand Osteoarthritis Working Group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies.* The Journal of rheumatology, 2015. **42**(11): p. 2190-2197.
203. Ruperto, N., et al., *Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis.* Rheumatology, 2003. **42**(12): p. 1452-1459.
204. Smith, C. and D. Betts, *The practice of acupuncture and moxibustion to promote cephalic version for women with a breech presentation: implications for clinical practice and research.* Complementary therapies in medicine, 2014. **22**(1): p. 75-80.
205. Wylde, V., et al., *Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set.* European Journal of Pain, 2015. **19**(5): p. 611-620.
206. Higgins JPT, G.S.e., *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration, 2011(Available from www.cochrane-handbook.org).
207. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.
208. Kirkham, J.J., et al., *Core outcome set–STAndards for reporting: the COS-STAR statement.* PLoS medicine, 2016. **13**(10): p. e1002148.
209. Furness, S., et al. *Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy*. Cochrane Database of Systematic Reviews, 2011. DOI: 10.1002/14651858.CD006386.pub3.
210. Glenny, A.-M., et al. *Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy*. Cochrane Database of Systematic Reviews, 2010. DOI: 10.1002/14651858.CD006387.pub2.
211. Bessell A, G.A., Furness S, Clarkson JE, Oliver R, Conway DI, Macluskey M, Pavitt S, Sloan P, Worthington HV, *Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment.* Cochrane Database of Systematic Reviews [serial on the internet], 2011(9).
212. Bourhis, J., et al., *Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: Results of a GORTEC randomized trial.* Radiotherapy and Oncology, 2011. **100**(1): p. 56-61.
213. Posner, M.R., et al., *Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.* New England Journal of Medicine, 2007. **357**(17): p. 1705-1715.
214. Gupta, D., et al. *A prospective comparison of sequential chemoradiation vs concurrent chemoradiation in locally advanced oropharyngeal carcinoma*. Cancer Biology and Therapy, 2009.
215. Olmi, P., et al., *Locoregionally advanced carcinoma of the oropharynx: Conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy - A multicenter randomized trial.* International Journal of Radiation Oncology Biology Physics, 2003. **55**(1): p. 78-92.
216. Rodriguez, M.O., et al., *Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck.* Cancer Biology and Therapy, 2010. **9**(5): p. 343-349.
217. Mitra, D., et al., *Chemoradiotherapy for advanced head and neck cancer - Analysis of a prospective, randomized trial.* Indian J Otolaryngol Head Neck Surg, 2006. **58**(4): p. 360-3.

218. Soo, K.C., et al., *Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison.* British Journal of Cancer, 2005. **93**(3): p. 279-286.
219. Haffty, B.G., et al., *Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: Final results of a randomized clinical trial.* International Journal of Radiation Oncology Biology Physics, 2005. **61**(1): p. 119-128.
220. Quon, H., et al., *Phase III study of radiation therapy with or without Cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: An intergroup trial of the Eastern Cooperative Oncology Group (E2382).* International Journal of Radiation Oncology Biology Physics, 2011. **81**(3): p. 719-725.
221. Zackrisson, B., et al., *Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma - The ARTSCAN study.* Radiotherapy and Oncology, 2011. **100**(1): p. 41-48.
222. Ackerstaff, A.H., et al., *Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer.* Head and Neck, 2012. **34**(7): p. 974-980.
223. Rischin, D., et al., *Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. **28**(18): p. 2989-2995.
224. Nutting, C.M., et al., *Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial.* Lancet Oncol, 2011. **12**(2): p. 127-36.
225. Gupta, T., et al., *Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial.* Radiotherapy and Oncology, 2012. **104**(3): p. 343-348.
226. Curran, D., et al., *Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab.* Journal of Clinical Oncology, 2007. **25**(16): p. 2191-2197.
227. Van Herpen, C.M.L., et al., *Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323).* British Journal of Cancer, 2010. **103**(8): p. 1173-1181.
228. Ackerstaff, A.H., et al., *First-year quality of life assessment of an intraarterial (radplat) versus intravenous chemoradiation phase III trial.* Head and Neck, 2009. **31**(1): p. 77-84.
229. Curran, D., et al., *Incomplete quality of life data in randomized trials: missing forms.* Statistics in medicine, 1998. **17**(5-7): p. 697-709.
230. Fayers, P.M., D. Curran, and D. Machin, *Incomplete quality of life data in randomized trials: missing items.* Statistics in Medicine, 1998. **17**(5-7): p. 679-696.
231. Hamel, J., et al., *What are the appropriate methods for analyzing patient-reported outcomes in randomized trials when data are missing?* Statistical methods in medical research, 2017. **26**(6): p. 2897-2908.
232. Coste, J., et al., *Non response, incomplete and inconsistent responses to self-administered health-related quality of life measures in the general population: patterns, determinants and*

impact on the validity of estimates — a population-based study in France using the MOS SF-36. Health and Quality of Life Outcomes, 2013. **11**: p. 44-44.
233. Mendenhall, W.M., et al., *Radiotherapy alone or combined with carbogen breathing for squamous cell carcinoma of the head and neck: A prospective, randomized trial.* Cancer, 2005. **104**(2): p. 332-337.
234. Hudis, C.A., et al., *Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system.* Journal of Clinical Oncology, 2007. **25**(15): p. 2127-2132.
235. Nadkarni, P.M. and C.A. Brandt, *The Common Data Elements for Cancer Research: Remarks on Functions and Structure.* Methods of information in medicine, 2006. **45**(6): p. 594-601.
236. Chari, A., et al., *Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes.* Journal of neurotrauma, 2016. **33**(13): p. 1212-1219.
237. Mokkink, L.B., et al., *The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes.* Journal of Clinical Epidemiology. **63**(7): p. 737-745.
238. Trotti, A., et al., *TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group.* Lancet Oncol, 2007. **8**(7): p. 613-24.
239. Miller, A.B., Hoogstraten, B., Staquet, M. and Winkler, A., *Reporting results of cancer treatment.* Cancer, 1981. **47**: p. 207-214.
240. Jensen, K., A.B. Jensen, and C. Grau, *The relationship between observer-based toxicity scoring and patient assessed symptom severity after treatment for head and neck cancer. A correlative cross sectional study of the DAHANCA toxicity scoring system and the EORTC quality of life questionnaires.* Radiotherapy and Oncology, 2006. **78**(3): p. 298-305.
241. Semple, C.J., et al., *Changes and challenges to patients' lifestyle patterns following treatment for head and neck cancer.* J Adv Nurs, 2008. **63**(1): p. 85-93.
242. Hudson, P. and S. Payne, *Family carers in palliative care*. 2008, Oxford: Oxford University Press.
243. Patterson, J., et al., *Head and neck cancer and dysphagia; caring for carers.* Psycho-Oncology, 2013. **22**(8): p. 1815-1820.
244. Hubbard, G., et al., *Treatment decision-making in cancer care: the role of the carer.* Journal of Clinical Nursing, 2010. **19**(13-14): p. 2023-2031.
245. Masterson, L., et al., *De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials.* European journal of cancer, 2014. **50**(15): p. 2636-2648.
246. Ollivier, L., et al., *Trade-off between Survival and Laryngeal Preservation in Advanced Laryngeal Cancer: The Otorhinolaryngology Patient's Perspective.* Annals of Otology, Rhinology & Laryngology, 2012. **121**(9): p. 570-575.
247. Van der Donk, J., et al., *Patient participation in clinical decision-making for treatment of T3 laryngeal cancer: a comparison of state and process utilities.* Journal of clinical oncology, 1995. **13**(9): p. 2369-2378.
248. McNeil, B.J., R. Weichselbaum, and S.G. Pauker, *Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer.* New England Journal of Medicine, 1981. **305**(17): p. 982-987.
249. Hamilton, D.W., et al., *Quality compared to quantity of life in laryngeal cancer: A time trade-off study.* Head & neck, 2016. **38**(S1).

250. Laccourreye, O., et al., *Total laryngectomy or laryngeal preservation for advanced laryngeal cancer. Impact of the functional risk upon the patient's preferences.* European annals of otorhinolaryngology, head and neck diseases, 2014. **131**(2): p. 93-97.
251. Sinha, I.P., R.L. Smyth, and P.R. Williamson, *Using the Delphi Technique to Determine Which Outcomes to Measure in Clinical Trials: Recommendations for the Future Based on a Systematic Review of Existing Studies.* PLOS Medicine, 2011. **8**(1): p. e1000393.
252. Hewlett, S., et al., *Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored.* Arthritis Care & Research, 2005. **53**(5): p. 697-702.
253. Sanderson, T., et al., *What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set.* Arthritis care & research, 2010. **62**(5): p. 640-646.
254. Kagawa-Singer, M., G.V. Padilla, and K. Ashing-Giwa. *Health-related quality of life and culture*. in *Seminars in oncology nursing*. 2010. Elsevier.
255. Sandelowski, M., *Sample size in qualitative research.* Research in nursing & health, 1995. **18**(2): p. 179-183.
256. Britten, N., *Qualitative research: qualitative interviews in medical research.* Bmj, 1995. **311**(6999): p. 251-253.
257. Valentine, G., *Doing household research: interviewing couples together and apart.* Area, 1999. **31**(1): p. 67-74.
258. Glaser, B.G., *The constant comparative method of qualitative analysis.* Social problems, 1965. **12**(4): p. 436-445.
259. Polkinghorne, D.E., *Language and meaning: Data collection in qualitative research.* Journal of counseling psychology, 2005. **52**(2): p. 137.
260. Centre, H.a.S.C.I., *National head and neck cancer audit 2014 - tenth annual report.* 2015.
261. Råheim, M., et al., *Researcher–researched relationship in qualitative research: Shifts in positions and researcher vulnerability.* International Journal of Qualitative Studies on Health and Well-being, 2016. **11**: p. 10.3402/qhw.v11.30996.
262. Greene, M.J., *On the inside looking in: Methodological insights and challenges in conducting qualitative insider research.* The qualitative report, 2014. **19**(29): p. 1-13.
263. Sharp, H.M., et al., *Patients' priorities among treatment effects in head and neck cancer: Evaluation of a new assessment tool.* Head & neck, 1999. **21**(6): p. 538-546.
264. Gill, S.S., et al., *Priorities for the Head and Neck Cancer Patient, their Companion and Members of the Multidisciplinary Team and Decision Regret.* Clinical Oncology, 2011. **23**(8): p. 518-524.
265. Kanatas, A., et al., *Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites.* European Archives of Oto-Rhino-Laryngology, 2013. **270**(3): p. 1067-1074.
266. List, M.A., et al., *Prioritizing treatment outcomes: Head and neck cancer patients versus nonpatients.* Head & Neck, 2004. **26**(2): p. 163-170.
267. McNeil , B.J., R. Weichselbaum , and S.G. Pauker *Speech and Survival.* New England Journal of Medicine, 1981. **305**(17): p. 982-987.
268. Tsevat, J., et al., *Health values of hospitalized patients 80 years or older.* Jama, 1998. **279**(5): p. 371-375.
269. List, M.A. and S.P. Bilir, *Functional outcomes in head and neck cancer.* Semin Radiat Oncol, 2004. **14**(2): p. 178-89.
270. Welsh, L.C., et al., *Neurocognitive Function After (Chemo)-Radiotherapy for Head and Neck Cancer.* Clinical Oncology. **26**(12): p. 765-775.

271. Dodd, R.H., L.A. Marlow, and J. Waller, *Discussing a diagnosis of human papillomavirus oropharyngeal cancer with patients: An exploratory qualitative study of health professionals.* Head Neck, 2016. **38**(3): p. 394-401.
272. Mease, P.J., et al., *Identifying the clinical domains of fibromyalgia: Contributions from clinician and patient delphi exercises.* Arthritis Care & Research, 2008. **59**(7): p. 952-960.
273. Serrano-Aguilar, P., et al., *Patient involvement in health research: a contribution to a systematic review on the effectiveness of treatments for degenerative ataxias.* Social science & medicine, 2009. **69**(6): p. 920-925.
274. Kirwan, J.R., et al., *Patient perspective on outcomes in rheumatology—a position paper for OMERACT 9.* The Journal of rheumatology, 2009. **36**(9): p. 2067-2070.
275. Blazeby, J., et al., *Core information set for oesophageal cancer surgery.* British Journal of Surgery, 2015. **102**(8): p. 936-943.
276. Mathers, J., et al., *Using qualitative research to understand what outcomes matter to patients: direct and indirect approaches to outcome elicitation.* Trials, 2015. **16**(S2): p. O39.
277. Sinha, I.P., et al., *Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people.* Trials, 2012. **13**(1): p. 1.
278. Bradburn, N.M. and W.M. Mason, *The effect of question order on responses.* Journal of Marketing Research, 1964: p. 57-61.
279. Sudman, S. and N.M. Bradburn, *Asking questions: a practical guide to questionnaire design.* 1983.
280. Harman, N.L., et al., *MOMENT–Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey.* Trials, 2013. **14**(1): p. 1.
281. Guyatt, G.H., et al., *GRADE guidelines: 2. Framing the question and deciding on important outcomes.* Journal of clinical epidemiology, 2011. **64**(4): p. 395-400.
282. Powell, C., *The Delphi technique: myths and realities.* J Adv Nurs, 2003. **41**(4): p. 376-82.
283. Devane, D., et al., *Evaluating maternity care: a core set of outcome measures.* Birth, 2007. **34**(2): p. 164-72.
284. Campbell, S.M., et al., *The Effect of Panel Membership and Feedback on Ratings in a Two-Round Delphi Survey: Results of a Randomized Controlled Trial.* Medical Care, 1999. **37**(9): p. 964-968.
285. Leape, L.L., et al., *Group judgments of appropriateness: the effect of panel composition.* International Journal for Quality in Health Care, 1992. **4**(2): p. 151-159.
286. Coulter, I., A. Adams, and P. Shekelle, *Impact of varying panel membership on ratings of appropriateness in consensus panels: a comparison of a multi-and single disciplinary panel.* Health services research, 1995. **30**(4): p. 577.
287. Macefield, R., et al., *Core outcome set development: the effect of Delphi panel composition and feedback on prioritisation of outcomes.* Trials, 2013. **14**(Suppl 1): p. P77-P77.
288. Goodman, C.M., *The Delphi technique: a critique.* Journal of advanced nursing, 1987. **12**(6): p. 729-734.
289. Brookes, S.T., et al., *Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development.* Trials, 2016. **17**(1): p. 409.
290. Rogers, S., F. Thomson, and D. Lowe, *The Patient Concerns Inventory integrated as part of routine head and neck cancer follow-up consultations: frequency, case-mix, and items initiated by the patient.* The Annals of The Royal College of Surgeons of England, 2018. **100**(3): p. 209-215.

291. List, M.A., et al., *Prioritizing treatment outcomes: head and neck cancer patients versus nonpatients.* Head Neck, 2004. **26**(2): p. 163-70.
292. Rogers, S., et al., *Health-related quality of life and clinical function after primary surgery for oral cancer.* British Journal of Oral and Maxillofacial Surgery, 2002. **40**(1): p. 11-18.
293. Mills, E.J., et al., *The quality of randomized trial reporting in leading medical journals since the revised CONSORT statement.* Contemp Clin Trials, 2005. **26**(4): p. 480-7.
294. Mailankody, S. and V. Prasad, *Overall survival in cancer drug trials as a new surrogate end point for overall survival in the real world.* JAMA Oncology, 2017. **3**(7): p. 889-890.
295. Burke, H.B., *Overall survival vs disease-specific survival.* JAMA Oncology, 2018. **4**(4): p. 586-586.
296. Hutcheson, K.A., et al., *Late dysphagia after radiotherapy-based treatment of head and neck cancer.* Cancer, 2012. **118**(23): p. 5793-5799.
297. Hutcheson, K.A., et al., *FUNCTIONAL OUTCOMES AFTER TORS FOR OROPHARYNGEAL CANCER: A SYSTEMATIC REVIEW.* European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, 2015. **272**(2): p. 463-471.
298. Awan, M.J., et al., *Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: A preliminary dosimetric comparison.* Oral Oncology, 2014. **50**(8): p. 746-752.
299. Langendijk, J.A., et al., *Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy.* Journal of clinical oncology, 2008. **26**(22): p. 3770-3776.
300. Nguyen, N.P., et al., *Combined chemotherapy and radiation therapy for head and neck malignancies.* Cancer, 2002. **94**(4): p. 1131-1141.
301. Lovell, S.J., et al., *Impact of dysphagia on quality-of-life in nasopharyngeal carcinoma.* Head & neck, 2005. **27**(10): p. 864-872.
302. Ringash, J. and A. Bezjak, *A structured review of quality of life instruments for head and neck cancer patients.* Head & Neck: Journal for the Sciences and Specialties of the Head and Neck, 2001. **23**(3): p. 201-213.
303. Whistance, R., et al., *A systematic review of outcome reporting in colorectal cancer surgery.* Colorectal Disease, 2013. **15**(10).
304. McCulloch, P., et al., *No surgical innovation without evaluation: the IDEAL recommendations.* The Lancet. **374**(9695): p. 1105-1112.
305. Kirkham, J.J., et al., *COS-STAR: a reporting guideline for studies developing core outcome sets (protocol).* Trials, 2015. **16**(1): p. 373.
306. McCulloch, P., et al., *No surgical innovation without evaluation: the IDEAL recommendations.* The Lancet, 2009. **374**(9695): p. 1105-1112.
307. Ergina, P.L., et al., *Challenges in evaluating surgical innovation.* The Lancet, 2009. **374**(9695): p. 1097-1104.
308. Barkun, J.S., et al., *Evaluation and stages of surgical innovations.* The Lancet, 2009. **374**(9695): p. 1089-1096.
309. Blencowe, N.S., et al., *Interventions in randomised controlled trials in surgery: issues to consider during trial design.* Trials, 2015. **16**(1): p. 392.
310. Prinsen, C.A., et al., *How to select outcome measurement instruments for outcomes included in a "Core Outcome Set"–a practical guideline.* Trials, 2016. **17**(1): p. 449.

311. Reeve, B.B., et al., *Recommended Patient-Reported Core Set of Symptoms to Measure in Adult Cancer Treatment Trials.* JNCI: Journal of the National Cancer Institute, 2014. **106**(7): p. dju129-dju129.
312. Chan, A.-W., et al., *SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials.* Bmj, 2013. **346**: p. e7586.
313. Programme), N.I.f.H.R.H.T.A.H.
314. of, E.M.A.G.o.t.c.i. and m.p.f.t.t.o. asthma.
315. Kirkham, J.J., M. Clarke, and P.R. Williamson, *A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials. gov: findings from a review of randomised controlled trials of rheumatoid arthritis.* bmj, 2017. **357**: p. j2262.
316. Clarke, M. and P. Williamson, *Core outcome sets and trial registries.* Trials, 2015. **16**(1): p. 216.
317. Barnes, K.L., et al., *Citation analysis did not provide a reliable assessment of core outcome set uptake.* Journal of Clinical Epidemiology.
318. Kirkham, J.J., et al., *Core Outcome Set–STAndards for Reporting: The COS-STAR Statement.* PLoS Med, 2016. **13**(10): p. e1002148.

Appendices

Appendix 1 The CONSENSUS Study protocol

Waters *et al. Trials* 2014, **15**:168
http://www.trialsjournal.com/content/15/1/168

STUDY PROTOCOL Open Access

The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer

Aoife MI Waters[1,2,3*], Catrin Tudur Smith[1], Bridget Young[4] and Terry M Jones[2,3]

Abstract

Background: The incidence of oropharyngeal cancer is increasing in the developed world. This has led to a large rise in research activity and clinical trials in this area, yet there is no consensus on which outcomes should be measured. As a result, the outcomes measured often differ between trials of comparable interventions, making the combination or comparison of results between trials impossible. Outcomes may also be 'cherry-picked', such that favourable results are reported, and less favourable results withheld. The development of a minimum outcome reporting standard, known as a core outcome set, goes some way to addressing these problems. Core outcome sets are ideally developed using a patient-centred approach so that the outcomes measured are relevant to patients and clinical practice. Core outcome sets drive up the quality and relevance of research by ensuring that the right outcomes are consistently measured and reported in trials in specific areas of health or healthcare.

Methods/Design: This is a mixed methods study involving three phases to develop a core outcome set for oropharyngeal cancer clinical trials. Firstly, a systematic review will establish which outcomes are measured in published oropharyngeal cancer randomised controlled trials (RCTs). Secondly, qualitative interviews with patients and carers in the UK and the USA will aim to establish which outcomes are important to these stakeholders. Data from these first two stages will be used to develop a comprehensive list of outcomes to be considered for inclusion in the core outcome set. In the third stage, patients and clinicians will participate in an iterative consensus exercise known as a Delphi study to refine the contents of the core outcome set. This protocol lays out the methodology to be implemented in the CONSENSUS study.

Discussion: A core outcome set defines a minimum outcome reporting standard for clinical trials in a particular area of health or healthcare. Its consistent implementation in oropharyngeal cancer clinical trials will improve the quality and relevance of research.

Trials and registration: This study is registered at the National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio, ID 13823 (17 January 2013).

Keywords: Core outcome set, Consensus, Delphi, Oropharyngeal cancer, Head and neck cancer

* Correspondence: aoife.waters@liverpool.ac.uk
[1]Department of Biostatistics, University of Liverpool, 1st Floor Duncan Building, Daulby Street, Liverpool L69 3GA, UK
[2]Department of Molecular and Clinical Cancer Medicine, Liverpool Cancer Research UK Centre, University of Liverpool, 200 London Road, Liverpool L3 9TA, UK
Full list of author information is available at the end of the article

Background

Around 1,500 cases of oropharyngeal squamous cell carcinoma (OPSCC) are diagnosed in the UK every year [1]. Treatment relies on radiotherapy (RT), surgery with or without post-operative RT or cisplatin-based chemoradiotherapy (CRT), CRT alone or following induction chemotherapy. Increasingly, small molecule adjuvants are also being used. Multi-modality therapy is associated, to varying degrees, with long-term deficits in speech and swallowing function, cosmesis and health-related quality of life.

While the incidence of squamous cancers at most subsites of the head and neck is decreasing, the incidence of OPSCC has doubled in the last decade; and this trend is seen throughout the developed world [2,3]. Oncogenic human papillomavirus type 16 (HPV-16) has been established as the causative agent and has given rise to a clinicopathologically distinct form of OPSCC that occurs in a younger patient population and is associated with improved survival outcomes, compared with HPV-negative disease [4,5].

Contemporary treatments for HPV-positive and HPV-negative OPSCC are, however, still the same and treatment survivors suffer from long-term sequelae of multi-modality therapy, to varying degrees. Clinical trials in HPV-positive disease are largely focused on deintensifying treatment to improve functional outcomes whilst maintaining the advantageous survival outcomes; however, current research in HPV-negative disease remains focused on improving survival outcomes, with less apparent focus on reducing toxicity and improving functional outcomes. This is largely due to the fact that overall survival rates for HPV-negative disease have remained stubbornly resistant to improvement for many decades.

Despite the fact that available treatments have a significant impact on functioning and quality of life, such outcomes are inconsistently measured and reported between trials. Additionally, there is no standardisation of outcome selection and reporting, even among trials of comparable interventions. This reduces the amount of data contributable for meta-analyses, leading to difficulties in interpreting treatment effect and in making evidence-based healthcare decisions. The development of a minimum outcome reporting standard for OPSCC clinical trials, known as a core outcome set, is one method proposed to address these problems.

A core outcome set defines the outcomes that should be consistently measured and reported in clinical trials in a specific area of health or healthcare. They are developed using consensus methods involving major stakeholders, such as patients and healthcare professionals, to ensure that the outcomes included are clinically relevant and therefore 'core'.

The existence of a core outcome set does not mean that only these outcomes should be measured; however, if a minimum outcome reporting standard is adhered to, then there will be greater consistency of reporting in clinical trials and a greater body of evidence to contribute to meta-analyses to inform healthcare decisions. Additionally, the risk of outcome reporting bias is lessened by ensuring that outcomes are consistently measured and reported.

The earliest efforts to improve outcome measurement in clinical trials were made by the Outcome Measures in Rheumatology (OMERACT) collaboration in the early 1990s [6]. This international network developed core sets of measures for most of the major rheumatological conditions, and an observational review by Kirkham *et al.* demonstrated an increase in the consistency of outcome reporting across clinical trials in rheumatoid arthritis (RA) in the years following publication of the RA core outcome set [7].

The OMERACT collaboration has actively involved patients in discussions about which outcomes to measure in trials since 2002 [8]. Patient involvement was first proposed at the OMERACT meeting in 2000 when participants considered what might be a 'clinically important change' in response to treatment. It was realised that the perspectives of patients are important in developing core outcome sets, and they have been actively involved in, and significantly contributed to, all subsequent OMERACT meetings. Patients have enriched the OMERACT research agenda, provided insights into patient participation in research and stimulated patient involvement in health outcomes research more broadly [9].

Other bodies are now recognising the importance of involving patients in trial research. INVOLVE, the national advisory group for the promotion and advancement of public involvement in NHS, public health and social care research, promotes the involvement of patients and the public in discussions about clinical trials because 'they are the participants in trials and ultimately the people for whom research is aimed to benefit' [10]. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative advocates the involvement of patients and the public in decisions about which outcomes should be included in core outcome sets in specific areas of health or healthcare.

The measurement of patient-reported outcomes (PROs) in clinical trials has increased substantially in the last 20 years [11]. These subjective measures help evaluate the burden of disease and treatment from the patient's perspective. The CONSORT group have recently published a PRO extension to their guidance that aims to improve the reporting of PROs in trials to facilitate the use of results in informing clinical practice and health policy [12].

Core outcome sets are now in development in a number of clinical areas and their use is advocated, in the UK, by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) and the Cochrane Collaboration [13,14]. Core outcome sets will only influence the evidence base if they are actually implemented, and as core outcome set developers we must therefore actively engage with trialists, Cochrane Review Groups, clinical guideline developers, research funders, journal editors, regulators and trial registries to act as advocates to ensure that their use is encouraged and supported.

Study overview

The objective of the CONSENSUS (Squamous Cell CarcinOma of the OropharyNx: Late PhaSE CliNical TrialS; Core OUtcomeS) Study is to develop a core outcome set for OPSCC clinical trials. This protocol presents the methodology to be used.

The first stage of the study will establish the current standard of outcome reporting in clinical trials through a systematic review of OPSCC randomised controlled trials (RCTs). The second stage will involve qualitative interviews with OPSCC patients and carers to establish which outcomes are important to these key stakeholders. The third part of the study will employ an iterative consensus technique known as a Delphi study. We expect that different stakeholder opinions about which outcomes should be measured in clinical trials in OPSCC will converge to achieve consensus on the outcomes in the OPSCC core outcome set.

Methods/Design

CONSENSUS is a mixed methods study. The Delphi questionnaire will be developed using a comprehensive list of outcomes identified from a systematic review, and outcomes identified from qualitative interviews with OPSCC patients and their carers.

Ethical approval for this study was granted in the UK by the Liverpool Central Research Ethics Committee (reference 12/NW/0708). Approval at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) was provided by the Institutional Review Board (protocol number 2013-0285).

Systematic review

A systematic review will identify which outcomes are reported in phase III RCTs of interventions for the treatment of OPSCC. This review will be limited to English language studies published in the last 10 years.

Search strategy

A broad-based search strategy will be used to identify all published OPSCC and squamous cell carcinoma of the head and neck (SCCHN) RCTs. This will be applied to PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 2003 to 14 May 2013 (Appendix A).

Types of studies and interventions

Any phase III RCT of a treatment for OPSCC with curative intent will be included. Only SCCHN trials that comprise patients with OPSCC will be included.

Types of participants

Adults aged over 18 years with OPSCC.

Exclusion criteria

Studies without OPSCC patients, studies involving patients with recurrent or metastatic disease, and studies of interventions for the treatment of the side-effects of treatment, such as xerostomia.

Eligibility of studies

Two reviewers (AW and a second reviewer) will independently assess the identified records. A large number of records will be identified by our search strategy, therefore studies will be excluded in three phases. All identified study titles will be reviewed and ineligible studies excluded. Studies that are eligible from the title or for which there is uncertainty will have their abstracts reviewed in the second phase. Again, studies that are eligible or for which there is uncertainty will have their full papers reviewed in the third phase.

In order to ensure accuracy of exclusion, a proportion of all included/excluded titles, abstracts and full papers will be reviewed by two senior authors (TMJ and CTS).

A proportion of the studies excluded by title will have their abstracts reviewed. If more than 1% of these studies are found to be eligible then a further proportion of the same amount will be reviewed, until 1% or less of further studies in the re-review sample are eligible.

Data extraction

Outcomes will be identified within the methods and results section of each paper, and for each outcome we will assess how it was defined and measured, the number of participants in which it was measured, whether it was measured using a validated tool, and whether it was stated in both the methods and results. The individual outcomes will be categorised under broader outcome domains.

Data analysis

All eligible studies will be tabulated, and the identified outcomes presented along with their definitions and method of measurement. We also wish to identify any heterogeneity in the definitions of outcomes and the way

in which they are measured. Scoping searches have suggested that outcomes with the same name are often defined or measured in different ways. We therefore wish to establish whether outcomes are defined and, if they are, whether there is heterogeneity in these definitions between studies which would make comparison of these outcomes between trials more difficult, if not impossible.

The identified outcomes will be categorised under broader outcome domains which will be decided upon by the study team. For functional outcomes, this process will be guided by the International Classification of Functioning, Disability and Health (ICF) categories for head and neck cancer [15].

Qualitative interviews

The objectives of the qualitative part of the study are to establish which outcomes are valued by patients and carers, and which outcomes they feel should be included in a core outcome set. The journey from diagnosis through treatment is often a turbulent one for patients with OPSCC and qualitative methods will be particularly useful in helping us to understand their experiences of treatment. Spouses will also be interviewed as they almost universally become carers to their partners during this time and can provide an expert witness account of events whilst helping to contextualise the importance of different outcomes.

Participants

Patients with OPSCC and their carers will be recruited to participate in qualitative interviews, from two centres in the UK and one in the USA. A carer is defined as a family member or spouse who provides informal care to the patient during their treatment and recovery. Patient and carer participants will be recruited from SCCHN survivorship clinics. Patient participants will be adults, aged 18 to 100 years, who are English speaking and up to 5 years post-treatment for OPSCC. Carers of eligible patient participants will also be invited to interview.

Eligible patients will be recruited from the outpatient clinic in a chronological order to avoid the risk that clinic staff will 'cherry-pick' patients who they anticipate will present a favourable account of their experiences. We will monitor the clinical and socio-demographic characteristics of our patient sample, and ensure maximum diversity in terms of the following characteristics: age, gender, sub-site, stage, HPV status, treatment modality and length of time since treatment. Maximum diversity sampling, a type of purposive sampling, is widely used in qualitative research with the aim of accessing a range of perspectives on the topic under investigation [16]. We will interview NHS patients in the UK, for whom care is provided free at the point of delivery and patients attending the University of Texas MD Anderson Cancer Center, which is a fee-paying institution. The UK and US groups will differ in their socio-economic circumstances, thus the sample encompasses diversity on this characteristic, which is well-recognised as having a significant impact on outcomes in SCCHN patients [17].

HPV status will not be available for patients whose diagnosis and treatment preceded testing for HPV. However, we will endeavour to recruit a mix of HPV-positive and HPV-negative patients.

We expect to recruit around 30 patients and carers in total, although this may change depending on early analyses.

Interview format

A semi-structured interview format will be used. Participants will be required to provide informed consent prior to interview. Conversation will be guided by a prompt guide of open-ended questions on topics such as diagnosis and treatment, and the effect the cancer and treatment had on participants' lives, both at the time of treatment and at the time of the interviews. Therefore, whilst the interview will be conversational in nature, discussion will be directed towards identifying outcomes of importance to patients and carers. Towards the end of the interviews we will directly ask participants which outcomes they think are most important and should be measured in clinical trials. Key to this interview technique is that it allows participants to explain their experience of the illness and treatment in their own terms, and to raise and focus on the aspects of their journey that are most important to them.

Interview analysis

In line with the principles of qualitative research, the analytical process will begin during data collection, as the data already gathered are analysed to inform the ongoing data collection. This will allow the study team to go back and refine questions, develop hypotheses, and pursue emerging avenues of inquiry in further depth in subsequent interviews [18].

We will take an interpretive approach, informed by the principles of the constant comparative method and by several procedural steps to ensure the quality of the analysis [19]. This involves an inductive process of identifying analytical categories as they emerge from the data (developing hypotheses from the ground or research field upwards rather defining them *a priori*). The analysis of patients' and carers' accounts will initially proceed in parallel, but related, courses. We shall analyse within each group for common themes, such as what is important to patients/carers, and how their lives have been affected by the cancer and treatment [20]. As the analysis develops we will compare across the different

groups to identify convergences and divergences. We will examine how participants present their accounts as well as the content of the interviews. That is, we will not simply take participants' accounts at face value.

We will compare data across the different groups (age, gender, sub-site, stage, HPV status, treatment modality, socio-economic status and length of time since treatment) and analyse for patterns in how these characteristics shape participants' priorities following cancer treatment. As the principal investigator (PI), AW will lead a process of 'cycling' between the developing analysis and new data, and the complete team will develop and 'test' the analysis by periodic discussion of transcripts and reports on the developing analysis. Initially, each transcript will be read several times by AW before developing open codes to describe each relevant unit of meaning. Initial open coding will occur at multiple levels, from detailed descriptions of experiences line by line, to the general stance participants take towards different aspects of their lives. Through comparison within and across the transcripts the open codes will gradually be developed into theoretical categories and subcategories, to reflect and test the developing analysis.

The categories will be organised into a framework to code and index the transcripts using NVivo qualitative data analysis software (version 10, 2012; QSR International Pty Ltd, Victoria, Australia). The framework categories will be continually checked and modified to ensure an adequate 'fit' with the data, whilst also accounting for variant or exceptional cases. The categories and the assignment of data to them will be reviewed by a second member of the project team.

The Delphi method

In order to gather opinion and to reduce the number of outcomes to a priority list for consideration in future OPSCC clinical trials we will use the Delphi method. This was originally developed by the RAND Corporation in the 1950s in order to forecast the influence of technology on warfare [21]. It is an iterative consensus technique which comprises sequential questionnaires answered anonymously by a panel of participants with relevant expertise [6].

Questioning takes place in rounds, and after each round of questions, an anonymous summary of the responses is fed back to the group. Individual participants may then decide to keep their original answers or to change their opinion in the subsequent round of voting. The advantage of this approach is that it is not face-to-face, and therefore avoids the problem of more vocal or apparently senior participants dominating the group discussion and therefore influencing others' voting.

In general, the range of answers decreases and the group converges towards a consensus opinion over the course of several rounds. The process terminates after a pre-defined stop criterion, which for this study will be whichever occurs first: reduction of the long list of outcomes to ten or less; or on completion of the second round of voting.

Synthesis of outcomes into Delphi questionnaire

Outcomes from systematic review

The outcomes highlighted in the systematic review will be categorised under broader outcome domains, and presented in the questionnaire as such.

Outcomes from interviews

Identifying measureable outcomes from the interview transcripts will be a more complex process. While some outcomes are likely to be obvious, the context must always be borne in mind, and it is important that our interpretation of the interview transcripts avoids either overlooking outcomes of importance to participants or misrepresenting them. For example, how extensively a participant talks about a particular aspect of their life is not necessarily indicative of its importance to them, since patients may talk about highly significant issues in a seemingly brief and casual manner as a way of managing their emotions. We will begin by analysing transcripts to identify experiences and priorities that map straightforwardly to obviously measurable outcomes. Examples include mouth dryness, difficulty swallowing and fatigue. Secondly, where a participant has described an experience or issue that was significant for them, the study team will attempt to map this to a measurable outcome. An example of this could be anxiety about survivorship clinic appointments, which is likely to be an expression of a patient's anxieties about recurrence and survival. One researcher (AW) will be responsible for making these interpretations, and two researchers (AW and BY) will review a proportion of the outcomes and the supporting evidence from the interview transcript to scrutinise and 'test' the plausibility of the interpretations involved in translating participants' accounts of their experiences and priorities into outcomes. Any uncertainties and a proportion of all outcomes derived through this process will be discussed with the whole study team (AW, CTS, BY, TMJ).

Patient interviews will be given primacy over the carer interviews in the analysis and derivation of outcomes. The carer acts as a witness to the patient's experience and therefore their accounts will be used largely to illuminate our analysis of the patient accounts. For example, we will identify how far carers confirm or refute patient accounts; where divergences arise we will return to the patient accounts to identify the reasons for these or

reconsider our interpretations as appropriate. The interview data will also be used to inform the presentation and labelling of outcomes, particularly for patients, in the Delphi study.

Participants

The Delphi study will survey individuals with a stake in clinical trials for OPSCC. This includes OPSCC patients and their carers, and healthcare professionals involved in the management of patients with OPSCC, namely, medical and surgical oncologists, speech and language therapists (SLTs), and head and neck clinical nurse specialists (CNSs). It is important that a proportion of our clinician participants are also involved in research or clinical trials; therefore, we will recruit medical and surgical oncologists and SLTs from a list of those involved in a multicentre SCCHN trial that is ongoing and coordinated by our unit, and CNSs through personal contacts and professional bodies.

In the UK, patient and carer interviewees will be approached about participation in the Delphi study at the time of the interview. Additional patient and carer participants will be identified within survivorship clinics. The Delphi questionnaire will be included with a postal invitation, and a follow-up telephone call will be made 7 days following postage to confirm that the questionnaire was received. Clinician participants will be invited by email to participate in an online Delphi questionnaire and a reminder email will be sent after 7 days. The invitation will clearly state the importance of completing all rounds of the Delphi study. Attrition is more likely in participants with minority opinions and this can lead to an overestimation of the degree of consensus in the final results [6]. It will be clearly stated that outcomes important to that individual may not be included in the final core outcome set.

Definition of consensus

This must be defined upfront to avoid consensus being defined in a way that could bias the results towards the beliefs of the research team. For an outcome to be included in the core outcome set there must be majority agreement of the critical importance of an outcome, and minority agreement that the outcome is not important. Conversely, for an outcome to be excluded there must be majority agreement that the outcome is not important, and only minority agreement that it is critically important. These judgements are based on GRADE Working Group recommendations and are discussed in further detail below [22,23].

Statistical considerations

There are no recommendations for the number of participants to include in a Delphi study. In a systematic review by Sinha *et al.* of studies using the Delphi method in core outcome set development, the number of participants ranged from 13 to 222 [6]. We have a heterogeneous group of participants and therefore our sample size will need to be slightly larger to account for the likely diversity of opinions [24]. We aim to recruit around 30 patients and carers, and 30 clinicians, who will be medical and surgical oncologists, SLTs, and head and neck CNSs.

Voting

In other Delphi studies a 'blank sheet' round has been used to canvas participant opinion and generate a comprehensive and inclusive list of candidate outcomes. However, in conducting the systematic review and interviews we have effectively completed this process.

Round 1

In round 1 of this Delphi study we will ask participants to rate each of the outcomes using the GRADE process, which suggests a 9-point scale (1 to 9) to rank their importance [23]. There will also be room for participants to add additional outcomes and to comment on why they have ranked outcomes as they have. Rankings of 7 to 9 indicate outcomes of critical importance, ratings of 4 to 6 represent outcomes that are important but not critical, while ratings of 1 to 3 are items that are deemed to be of limited importance. All outcomes will be carried through to the second round with first round scores displayed for each outcome. Consensus to carry an outcome through to the core outcome set will be defined as more than 70% of participants scoring its importance as 7 to 9 and less than 15% scoring it as 1 to 3. Additional outcomes will be coded by the study team using the same methods as for the interview and systematic review. Feedback will be analysed using software adapted from another Delphi study.

Round 2

The number and percentage of participants that allocated each score will be presented to participants. However, feedback to each group will be randomised such that some participants receive only their group's voting and others receive both groups' voting. Participants will then be asked to rate the outcomes again, using the 9-point scale.

Analysis of voting

The opinions of different groups can be analysed either together or separately. Differences in opinion can be accounted for by having separate panels for different stakeholder groups [25]. It is not clear at this stage whether patients and carers will have different opinions to healthcare professionals. Macefield *et al.*, in using a

Delphi study to develop a core outcome set, demonstrated that the way in which feedback is delivered to participants affects the voting in subsequent rounds [26]. Feedback was randomised such that a proportion of both stakeholder groups received feedback from both stakeholder groups, and not just their own group. This altered voting, especially by the clinician group. We will randomise feedback such that half of the patient/carer group will receive results from the patients'/carers' first round of voting, and half will receive results from patients/carers and clinicians. Similarly, half of the clinicians will receive results of the clinicians' voting in the first round, and half will receive feedback from both patients/carers and clinicians. It is important to ensure that we have similar numbers between the panels for every round so that the final consensus is not numerically dominated by one group's responses. As recommended by Sinha *et al.*, we will report a measure of the distribution of scores for each outcome considered in the final round [6]. This is because cut-off scores, used in most studies, do not describe how strongly the minority feel, and so an apparent consensus could actually be masking major disagreement within the group [27].

Consensus meeting

After round 2, the remaining outcomes will be reviewed. If consensus has not been reached or there is significant disagreement between the groups, we will conduct a face-to-face meeting of 15 Delphi participants who are key stakeholders (patients, carers, medical and surgical oncologists, SLTs, and CNSs) to resolve any disagreement, and discuss the remaining outcomes and their application within clinical trials. By the end of this process we should have identified 'what' outcomes to measure, although we may well not be clear on the best way of measuring these.

Discussion

A core outcome set for OPSCC will improve the conduct, reporting and contribution of clinical trials to the existing body of evidence for OPSCC in the published literature. We believe that establishing which outcomes to measure takes priority over establishing how to measure these outcomes as any recommendation regarding a specific instrument may well become outdated.

As stated previously, a core outcome set will only have impact if it is consistently implemented in trials. We must actively engage with trialists, regulators, and those that fund and publish trials to ensure that our core outcome set is used, and that there are incentives to use it, not just in the UK but in the rest of the academic world.

Trial status

We are preparing to recruit participants to the Delphi study.

Appendix A

Search strategies for systematic review

PubMed search strategy: 1 January 2003 to 14 May 2013

1. "Oropharyngeal Neoplasms"[Mesh]
2. ("Head and Neck Neoplasms"[Mesh:NoExp])
3. "Otorhinolaryngologic Neoplasms"[Mesh:NoExp]
4. "Pharyngeal Neoplasms"[Mesh:NoExp]
5. "Neoplasms"[Mesh]
6. (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* OR SCC)
9. (#5 OR #6)
10. "Oropharynx"[Mesh]
11. (oropharyn* OR mesopharyn* OR tonsil* OR "head and neck" OR "head neck" OR "head-neck" OR "head-and-neck" OR "tongue base" OR "soft palate")
12. (#10 OR #11)
13. (#9 AND #12)
14. (HNSCC ORSCCHN OR OP-SCC OR OPSCC)
15. (#1 OR #2 OR #3 OR #4 OR #13 OR #14)
16. ((((Randomized Controlled Trial[ptyp])) OR ((Controlled Clinical Trial[ptyp])) OR ((Clinical Trial [ptyp])) OR ("Clinical Trials as Topic"[Mesh]) OR ("Clinical Trials, Phase III as Topic"[Mesh]) OR ("Clinical Trials, Phase IV as Topic"[Mesh]) OR ("Controlled Clinical Trials as Topic"[Mesh]) OR ("Clinical Trial"[Publication Type]) OR ("Controlled Clinical Trial"[Publication Type]) OR ("Clinical Trial, Phase III"[Publication Type]) OR ("Clinical Trial, Phase IV"[Publication Type]) OR ("Multicenter Study"[Publication Type]) OR ("Multicenter Studies as Topic"[Mesh]) OR ("Random Allocation"[Mesh]) OR ("Double-Blind Method"[Mesh]) OR ("Single-Blind Method"[Mesh]) OR ("Cross-Over Studies"[Mesh]) OR ("Placebos"[Mesh]) OR (controlled[tiab] AND (trial[tiab] OR trials[tiab] OR study[tiab] OR studies[tiab])) OR (blind[tiab] OR blinding[tiab] OR blinded[tiab] OR mask[tiab] OR masking[tiab] OR masked[tiab] OR placebo [tiab] OR placebos[tiab] OR rct[tiab] OR random [tiab] OR randomised[tiab] OR randomized[tiab] OR randomly[tiab] OR randomisation[tiab] OR randomization[tiab]) OR (factorial[tiab]) OR (divided [tiab] AND (group[tiab] OR groups[tiab])) OR (crossover[tiab]) OR ("cross over"[tiab]) OR (multicentre[tiab] OR multicentred[tiab] OR multicentric [tiab]) OR (versus[ti] OR vs[ti]) OR ("treatment arm"[tiab]) OR ("phase III"[tiab] OR "phase three" [tiab] OR "phase 3"[tiab]) OR ("latin square"[tiab]) NOT (("Animals"[Mesh] OR mouse[ti] OR mice[ti] OR pig[ti] OR pigs[ti] OR rat[ti] OR rats[ti] OR rabbit*[ti]) NOT ("Animals"[Mesh] OR mouse[ti] OR mice[ti] OR pig[ti] OR pigs[ti] OR rat[ti] OR rats [ti] OR rabbit*[ti] OR cadaver[ti] OR cadavers[ti]) AND ("Humans"[Mesh])))))

17. (#15 AND #16)
18. ""Cochrane Database Syst Rev""[Journal]
19. ("systematic review" OR "meta analysis")
20. (#19 OR #18)
21. (#17 NOT #20)

Cochrane Central Register of Controlled Trials (CENTRAL): 1 January 2003 to 14 May 2013

1. MeSH descriptor: [Oropharyngeal Neoplasms] explode all trees
2. MeSH descriptor: [Head and Neck Neoplasms] this term only
3. MeSH descriptor: [Pharyngeal Neoplasms] this term only
4. MeSH descriptor: [Otorhinolaryngologic Neoplasms] this term only
5. MeSH descriptor: [Neoplasms] explode all trees
6. cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* OR SCC
7. #5 OR #6
8. MeSH descriptor: [Oropharynx] explode all trees
9. oropharyn* OR mesopharyn* OR tonsil* OR "head and neck" OR "head neck" OR "head-neck" OR "head-and-neck" OR pharyn* OR "tongue base" OR "soft palate"
10. #8 OR #9
11. #7 AND #10
12. HNSCC OR SCCHN OR OP-SCC OR OPSCC
13. #1 OR #2 OR #3 OR #4 OR #11 OR #12

Embase: 1 January 2003 to 14 May 2013

1. Exp Oropharynx tumor/
2. Pharynx cancer/
3. Neoplasm/
4. (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* OR SCC).tw.
5. #3 OR #4
6. exp OROPHARYNX/OR exp OROPHARYNX CANCER/OR exp OROPHARYNX CARCINOMA/
7. (oropharyn* OR mesopharyn* OR tonsil* OR "head and neck" OR "head neck" OR "head-neck" OR"head-and-neck" OR pharyn* OR "tongue base" OR "soft palate").tw.
8. #6 OR #7
9. #5 AND #8
10. (HNSCC OR SCCHN OR OP-SCC OR OPSCC).tw.
11. #1 OR #2 OR #9 OR #10
12. (random* OR factorial* OR placebo* OR assign* OR allocat*).mp. OR crossover*.tw. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. (cross adj over*).tw.
14. (cross adj over*).tw.
15. ((blind* OR mask*) and (single OR double OR triple OR treble)).tw.
16. (treatment adj arm*).tw.
17. (control* adj group*).tw.
18. (phase adj III).mp. OR three.tw. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. (versus OR vs).tw.
20. rct.tw.
21. CROSSOVER PROCEDURE/
22. DOUBLE BLIND PROCEDURE/
23. SINGLE BLIND PROCEDURE/
24. RANDOMIZATION/
25. PLACEBO/
26. exp CLINICAL TRIAL/
27. PARALLEL DESIGN/
28. LATIN SQUARE DESIGN/
29. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
30. #11 AND #29
31. limit #30 to human
32. "systematic review".tw.
33. #31 NOT #32

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials; CNS: Clinical nurse specialist; COMET: Core Outcome Measures in Effectiveness Trials; CRT: Chemoradiotherapy; HPV: Human papillomavirus; HPV-16: Human papillomavirus type 16; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; NHS: National Health Service; NIHR: National Institute for Health Research; OMERACT: Outcome Measures in Rheumatology; OPSCC: Oropharyngeal squamous cell carcinoma; PI: Principal investigator; PRO: Patient-reported outcome; RA: Rheumatoid arthritis; RCT: Randomised controlled trial; RT: Radiotherapy; SCCHN: Squamous cell carcinoma of the head and neck; SLT: Speech and language therapist.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AW conceived and designed the study, and wrote the manuscript. CTS conceived and designed the study, and provided critical revision of the manuscript. BY conceived and designed the study, and provided critical revision of the manuscript. TMJ conceived and designed the study, and provided critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank Drs Kate Hutcheson and Jo Patterson for their collaboration in the qualitative part of the study, and the British Association of Head & Neck Oncologists and The Royal Society of Medicine for grants to fund travel to the University of Texas MD Anderson Cancer Center. AW is supported by the Medical Research Council (grant number G0800792) via the North West Hub for Trials Methodology Research.

Author details

[1]Department of Biostatistics, University of Liverpool, 1st Floor Duncan Building, Daulby Street, Liverpool L69 3GA, UK. [2]Department of Molecular and Clinical Cancer Medicine, Liverpool Cancer Research UK Centre, University of Liverpool, 200 London Road, Liverpool L3 9TA, UK. [3]Department of Otolaryngology - Head and Neck Surgery, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK. [4]Department of Psychological Sciences, University of Liverpool, Whelan Building, Brownlow Hill, Liverpool L69 3GB, UK.

Received: 4 March 2014 Accepted: 17 April 2014
Published: 13 May 2014

References

1. Cancer Research UK: *Number of New Cases of Oral Cancer (C00-C06, C09-C10, C12-C14), By Subsite, UK, 2010*; 2010 [http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/incidence/#source1]
2. Price G, Roche M, Crowther R, Wright R: *Profile of head and neck cancers in England: incidence, mortality and survival.* Oxford: Oxford Cancer Intelligence Unit; 2010.
3. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML: **Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers.** *J Clin Oncol* 2013, **31**(36):4550–4559.
4. Shaw R, Robinson M: **The increasing clinical relevance of human papillomavirus type 16 (HPV-16) infection in oropharyngeal cancer.** *Br J Oral Maxillofac Surg* 2011, **49**(6):423–429.
5. Ragin CCR, Taioli E: **Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis.** *Int J Canc* 2007, **121**(8):1813–1820.
6. Sinha IP, Smyth RL, Williamson PR: **Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies.** *PLoS Med* 2011, **8**(1):e1000393.
7. Kirkham J, Boers M, Tugwell P, Clarke M, Williamson P: **Outcome measures in rheumatoid arthritis randomised trials over the last 50 years.** *Trials* 2013, **14**(1):324.
8. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L: **OMERACT: an international initiative to improve outcome measurement in rheumatology.** *Trials* 2007, **8**(1):38.
9. Kirwan JR, de Wit M: **What have we learned from a decade of patient involvement in OMERACT and its effect on trial outcome assessments?** *Trials* 2011, **12**(Suppl 1):A80.
10. Denegri S, Buckland S: *INVOLVE response to Commons Select Committee Inquiry into clinical trials.* Eastleigh: INVOLVE; 2013.
11. Sanders C, Egger M, Donovan J, Tallon D, Frankel S: **Reporting on quality of life in randomised controlled trials: bibliographic study.** *BMJ* 1998, **317**(7167):1191–1194.
12. Calvert M, Brundage M, Jacobsen P, Schunemann H, Efficace F: **The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice.** *Health Qual Life Outcomes* 2013, **11**(1):184.
13. Williamson P, Clarke M: **The COMET (Core Outcome Measures in Effectiveness Trials) initiative: its role in improving cochrane reviews.** *Cochrane Database Syst Rev* 2012, **5**:ED000041.
14. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P: **Developing core outcome sets for clinical trials: issues to consider.** *Trials* 2012, **13**(1):132.
15. Tschiesner U, Rogers S, Dietz A, Yueh B, Cieza A: **Development of ICF core sets for head and neck cancer.** *Head Neck* 2010, **32**(2):210–220.
16. Coyne IT: **Sampling in qualitative research: purposeful and theoretical sampling; merging or clear boundaries?** *J Adv Nurs* 1997, **26**(3):623–630.
17. Molina MA, Cheung MC, Perez EA, Byrne MM, Franceschi D, Moffat FL, Livingstone AS, Goodwin WJ, Gutierrez JC, Koniaris LG: **African American and poor patients have a dramatically worse prognosis for head and neck cancer.** *Cancer* 2008, **113**(10):2797–2806.
18. Catherine P, Sue Z, Nicholas M: **Analysing qualitative data.** *BMJ* 2000, **320**(7227):114–116.
19. Glaser BG: **The constant comparative method of qualitative analysis.** *Soc Probl* 1965, **12**(4):436–445.
20. Polkinghorne DE: **Narrative configuration in qualitative analysis.** *Int J Qual Stud Educ* 1995, **8**(1):5–23.
21. Dalkey N, Helmer O: **An experimental application of the Delphi method to the use of experts.** *Manag Sci* 1963, **9**(3):458–467.
22. Jaeschke R, Guyatt GH, Dellinger P, Schünemann H, Levy MM, Kunz R, Norris S, Bion J, GRADE Working Group: **Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive.** *BMJ* 2008, **337**:a744.
23. **GRADE handbook for grading quality of evidence and strength of recommendation.** Edited by Schünemann H, Brozek J, Oxman. : Version 3.2. The GRADE Working Group; 2009.
24. Skulmoski GJ, Hartman FT, Krahn J: **The Delphi method for graduate research.** *J Inf Technol Educ* 2007, **6**:1–21.
25. Mease PJ, Arnold LM, Crofford LJ, Williams DA, Russell IJ, Humphrey L, Abetz L, Martin SA: **Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises.** *Arthritis Care Res* 2008, **59**(7):952–960.
26. Macefield R, Blencowe N, Brookes S, Jacobs M, Sprangers M, Williamson P, Blazeby J: **Core outcome set development: the effect of Delphi panel composition and feedback on prioritisation of outcomes.** *Trials* 2013, **14**(Suppl 1):77.
27. Goodman CM: **The Delphi technique: a critique.** *J Adv Nurs* 1987, **12**(6):729–734.

doi:10.1186/1745-6215-15-168
Cite this article as: Waters *et al.*: The CONSENSUS study: protocol for a mixed methods study to establish which outcomes should be included in a core outcome set for oropharyngeal cancer. *Trials* 2014 **15**:168.

Appendix 2 Pubmed search strategy

Search criteria	Search terms
Oropharyngeal squamous cell carcinoma	1. "Oropharyngeal Neoplasms"[Mesh]
	2. ("Head and Neck Neoplasms"[Mesh:NoExp])
	3. "Otorhinolaryngologic Neoplasms"[Mesh:NoExp]
	4. "Pharyngeal Neoplasms"[Mesh:NoExp]
Cancer	5. "Neoplasms"[Mesh]
	6. (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* OR SCC)
Oropharynx	9. (#5 OR #6)
	10. "Oropharynx"[Mesh]
	11. (238arbogen238x* OR mesopharyn* OR tonsil* OR"head and neck" OR "head neck" OR "head-neck" OR "head-and-neck" OR "tongue base" OR "soft palate")
	12. (#10 OR #11)
	13. (#9 AND #12)
	14. (HNSCC ORSCCHN OR OP-SCC OR OPSCC)
	15. (#1 OR #2 OR #3 OR #4 OR #13 OR #14)
Randomized controlled trials (Cochrane Highly Sensitive Search Strategy)	16. ((((Randomized Controlled Trial[ptyp])) OR((Controlled Clinical Trial[ptyp])) OR ((Clinical Trial [ptyp])) OR ("Clinical Trials as Topic"[Mesh]) OR ("Clinical Trials, Phase III as Topic"[Mesh]) OR ("Clinical Trials, Phase IV as Topic"[Mesh]) OR ("Controlled Clinical Trials as Topic"[Mesh]) OR ("Clinical Trial"[Publication Type]) OR ("Controlled Clinical Trial"[Publication Type]) OR ("Clinical Trial, Phase III"[Publication Type]) OR ("Clinical Trial, Phase IV"[Publication Type]) OR ("Multicenter Study"[Publication Type]) OR ("Multicenter Studies as Topic"[Mesh]) OR ("Random Allocation"[Mesh]) OR ("Double-Blind Method"[Mesh]) OR ("Single-Blind Method"[Mesh]) OR ("Cross-Over Studies"[Mesh]) OR ("Placebos"[Mesh]) OR (controlled[tiab] AND (trial[tiab] OR trials[tiab] OR study[tiab] OR studies[tiab])) OR (blind[tiab] OR blinding[tiab] OR blinded[tiab] OR mask[tiab] OR masking[tiab] OR masked[tiab] OR placebo [tiab] OR placebos[tiab] OR rct[tiab] OR random [tiab] OR randomised[tiab] OR randomized[tiab] OR randomly[tiab] OR randomisation[tiab] OR randomization[tiab]) OR (factorial[tiab]) OR (divided [tiab] AND (group[tiab] OR groups[tiab])) OR (crossover[tiab]) OR ("cross over"[tiab]) OR (multicentre[tiab] OR multicentred[tiab] OR multicentric [tiab]) OR (versus[ti] OR vs[ti]) OR ("treatment arm"[tiab]) OR ("phase III"[tiab] OR "phase three" [tiab] OR "phase 3"[tiab]) OR ("latin square"[tiab]) NOT (("Animals"[Mesh] OR mouse[ti] OR mice[ti] OR pig[ti] OR pigs[ti] OR rat[ti] OR rats[ti] OR rabbit*[ti]) NOT (("Animals"[Mesh] OR mouse[ti] OR mice[ti] OR pig[ti] OR pigs[ti] OR rat[ti] OR rats [ti] OR rabbit*[ti] OR cadaver[ti] OR cadavers[ti]) AND
To exclude systematic reviews	

	(“Humans”[Mesh]))))) 17. (#15 AND #16) 18. ““Cochrane Database Syst Rev”“[Journal] 19. (“systematic review” OR “meta analysis”) 20. (#19 OR #18) 21. (#17 NOT #20)

Appendix 3 Characteristics of included studies

Author	Country	Randomized patients	Arm A intervention	Arm B intervention	Arm C intervention	Number of outcomes	Outcomes measured
Adelstein, 2003 [1]	USA	295	RT alone	RT + Cisplatin	RT (Split Course) + Cisplatin/ 5FU	5	AT, OS, CRR, DSS, RP
Asif R, 2003 [2]	India	60	RT alone	RT + Cisplatin		2	AT,R
Grau, 2003 [3]	Multinational	478	RT	RT + Mitomycin C		5	AT, LT, OS, LRC, CanSS
Olmi, 2003 [4]	Italy	192	Conventional RT	Split-course accelerated fractionated RT (S-AHF)	Conventional RT + concomitant CT	5	AT, LT,OS, DFS, EFS
Smid, 2003, Zakotnik, 2007 [5, 6]	Slovenia	114	Surgery + RT	Surgery + RT + Concomitant MMC + Bleomycin		7	AT, LT, OS, LRC, DFS, DM, SPM
Bernier, 2004 [7]	European	334	Radical Surgery + RT	Radical Surgery + RT + Cisplatin		7	AT, LT, OS, PFS, DM, Rel, SPT
Cooper, 2004, Cooper, 2012 [8] [9]	USA	459	Surgery + RT	Surgery + RT + Concurrent Cisplatin		6	AT, LT, OS, LRC, DFS, CauSS
Fountzilas, 2004 [10]	Multinational	128	RT alone	RT + Concomitant Cisplatin	RT + Concomitant Carboplatin	5	AT, OS, CRR, DurCR, TTP
Huguenin, 2004, Ghadjar,	European	224	RT + Chemo	RT alone		7	AT, LT, OS, TTF, CanSS, TLRF, TDMR

2012 [11, 12]							
Olasz, 2004 [13]	Hungary	38	Bleomycin, Vincristine, Methotrexate + Surgery	Bleomycin, Vincristine, Methotrexate, Cisplatin + Surgery		10	AT, OS, R, DFS, DM, SPM, LR,RR, LRR, PR
Budach, 2005 [14]	German	384	Hyperfractionated Accelerated RT	Hyperfractionated Accelerated CRT		6	AT, LT, OS, LRC, PFS, FDM
Ezzat, 2005 [15]	Egypt	60	Conventioal RT 5F/week	Accelerated RT 6F/week	Accelerated RT + Mitomycin C	7	AT, LT, OS, LRC, R, DM, LC
Haffty, 2005 [16]	USA	128	Concurrent CRT + MC	Concurrent CRT + POR		8	AT, LT, OS, DFS, CauSS, MFS, LRRFS, LRFS
Hitt, 2005 [17]	Spain	387	Induction cisplatin and 5FU + CRT	Induction paclitaxel, cisplatin and 5FU + CRT		6	AT, OS, TTF, OPR, OCR, TRS
Mendenhall, 2005 [18]	USA	101	RT alone	RT + Carbogen		7	AT, OS, LRC, LC, CauSS, MFS, PBCB
Sanguineti, 2005 [19]	Italy	226	Surgery + conventional fractionation RT	Surgery + accelerated RT		4	AT, LT, OS, LRC
Soo, 2005 [20]	Singapore	119	Concurrent CRT (Cisplatin/5FU) +/- salvage ND	Radical Surgery + adjuvant RT		3	AT, OS, DFS
Bensadoun, 2006 [21]	France	171	Cisplatin + 5FU + concomitant twice-daily RT	Twice-daily RT alone		12	AT, LT, OS, LRC, R, DFS, PFS, LC, ED, GT, SS, SC
Bonner, 2006, Curran, 2007,	Multinational	424	RT alone	RT + Cetuximab		8	AT, LT, OS, LRC, R, PFS, HR-QOL, S

Bonner, 2010 [22-24]							
Bourhis, 2006 [25]	France	268	Accelerated RT	Conventional RT		6	AT, LT, OS, LRC, DFS, H
Mitra, 2006 [26]	India	180	Induction Cis + 5FU > RT	RT alone		6	AT, LT, OS, R, DFS, LC
Posner, 2007 [27]	TAX 324	501	TPF + CRT	PF + CRT		5	AT, LT, OS, R, PFS
Vermorken, 2007, van Herpen, 2010 [28, 29]	European EORTC 24971/TAX 323	358	TPF (Docetaxel, Cisplatin, 5-fu) +/- RT	PF +/- RT		8	AT, LT, OS, R, PFS, HR-QOL, TTF, DurR
Argiris, 2008 [30]	USA	76	Surgery + RT	Surgery + RT + Carboplatin		4	AT, OS, DFS, PoF
Ghoshal, 2008 [31]	India	290	Concomitant boost RT	Conventional RT		6	AT, LT, LRC, R, DFS, PoF
Racadot, 2008 [32]	France	146	Surgery + RT	Surgery + CRT (Carboplatin)		6	AT, LT, OS, LRC, MCR, PF
Sarkar, 2008 [33]	India	72	Conventional RT + Cisplatin	Conventional RT + Vinorelbine		3	AT, LT, R
Suwinski, 2008 [34]	Poland	279	Surgery + Conventional RT 5 days/week	p-CAIR, Surgery + conventional RT, 7 days a week		6	AT, LT, OS, LRC, MFS, SCFS
Gupta, 2009 [35]	India	105	Induction Cisplatin + 5FU > low dose weekly cisplatin	CRT		4	AT, OS, R, DFS

Rasch, 2010, Ackertsaff, 2009, Ackertaff, 2012 [36-38]	The Netherlands and New Zealand	239	Inta-aterial cisplatin, standard RT	Intra-venous cisplatin, standard RT		9	AT, OS, LRC, R, DFS, HR-QOL, LC, MFS, DSS
Grazia, 2010 [39]	Italy	164	RT	RT + Concurrent daily low dose carboplatin		6	AT, LT, OS, R, DFS, LRRFS
Rischin, 2010 [40]	Multinational	861	RT + Cisplatin	RT + Cisplatin and Tirapazamine		6	AT, LT, OS, HR-QOL, FFS, TLRF
Rodriguez, 2010 [41]	Cuba	106	RT + Nimotuzumab	RT + placebo		5	AT, HR-QOL, CRR, Imm, SB
Bourhis, 2011 [42]	France	109	Very accelerated RT 64Gy/ 32 frctns of 2Gy in 23 days (2Gy/ frctn BD)	RT-CT 62-64 Gy/5 weeks and 31-32 frctns (1/52 rest after each Rx week and 2Gy/frctn BD)		5	AT, LT, OS, EFS,H
Hamed, 2011 [43]	Egypt	52	RT + Concurrent paclitaxel	RT + Concurrent cisplatin		6	AT, OS, LRC, R, PFS, LRFS
Nutting, 2011 [44]	UK	94	Conventional RT	IMRT		6	AT, LT, OS, HR-QOL, X, LRPFS
Quon, 2011 [45]	USA	371	RT	RT + Cisplatin		7	AT, LT, OS, R, FFS, LO, NT
Zackrisson, 2011 [46]	Sweden	750	Conventional fractionation RT alone	Accelerated fractionation RT alone		8	AT, LT, OS, LRC, HR-QOL, CauSS, IVDVD, VODS
Bourhis, 2012 [47]	European	840	Conventional CRT (carboplatin +5FU)	Accelerated CRT (carboplatin +5FU)	Very accelerated RT	6	AT, LT, OS, PFS, DM, LRP

Gupta, 2012 [48]	India	62	3D-CRT	IMRT		6	AT, LT, OS, LRC, PoF, ASGT
Halim, 2012 [49]	Egypt	216	RT + Concomitant weekly low dose gemcitabine	RT + Concomitant weekly low does paclitaxel		5	AT, LT, OS, R, PFS
Haddad, 2013 [50]	Multinational	145	Induction CT > concurrent CRT	Concurrent CRT		3	AT, OS, PFS
Skladowski, 2013 [51]	Poland	345	Concomitant accelerated boost	Continous accelerated irradiation		6	AT, LT, OS, LRC, DM, SPM

Abbreviations:

Toxicity outcomes ASGT= acute salivary gland toxicity; AT= acute toxicity; GT= gastrostomy tube; LT= late toxicity; LO= laryngeal oedema; H= Hospitalisation; NT= nutritional toxicity; OPR= organ preservation rate; S= safety; X= xerostomia

Survival outcomes CanSS= cancer-specific survival; CauSS= cause-specific survival; DFS= disease-free survival; DSS= disease-specific survival; FFS= failure-free survival; ED= early death; EFS= Event-free survival; LRFS= local recurrence-free survival; LRPFS= loco-regional progression-free survival; LRRFS= loco-regional recurrence free survival; MFS= metastasis-free survival; OS=overall survival; PFS= Progression-free survival; SB= survival benefit; SCFS= second cancer-free survival; SS= specific survival

Disease control CRR= complete response rate; DM= distant metastases; DurCR= duration of complete response; DurR= duration of response; FDM= freedom from distant metastases; LARR= local and regional recurrence; LC= local control; LR= local recurrence; LRC= loco-regional control; LRP= loco-regional progression; MCR= metastasis control rates; OCR= overall control rate; RP= recurrence patterns; R= response; Rel= relapse; RR= regional recurrence; SC= systemic control; SPM= second primary malignancy; SPT= second primary tumour; TDMR= time to distant metastatic relapse; TLRF= time to loco-regional failure; TTF= time to treatment failure; TTP= time to progression

Quality of life HR-QOL= health-related quality of life;

Other PBCB= Identification of parameters that might predict a benefit from carbogen breathing; Imm= Immunogenicity; IVDVD= Influence of variations in dose–volume distributions in targets and critical organ volumes on the outcome regarding both disease and morbidity; PF= prognostic factors; PoF= patterns of failure; PR= pathological response; TRS= time to radical surgery; VODS= Variations in outcome in different sub-sites and stages with respect to treatment type

References for systematic review studies

1. Adelstein, D.J., et al., *An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2003. **21**(1): p. 92-98.
2. Asif, R., et al., *Concurrent cisplatin and radiotherapy in advanced head and neck cancer.* Indian Journal of Otolaryngology and Head and Neck Surgery, 2003. **55**(2): p. 94-96.
3. Grau, C., et al., *Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: Results of the IAEA multicentre randomised trial.* Radiotherapy and Oncology, 2003. **67**(1): p. 17-26.
4. Olmi, P., et al., *Locoregionally advanced carcinoma of the oropharynx: Conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy - A multicenter randomized trial.* International Journal of Radiation Oncology Biology Physics, 2003. **55**(1): p. 78-92.
5. Smid, L., et al., *Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma.* International Journal of Radiation Oncology Biology Physics, 2003. **56**(4): p. 1055-1062.
6. Zakotnik, B., et al., *Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin.* International Journal of Radiation Oncology Biology Physics, 2007. **67**(3): p. 685-690.
7. Bernier, J., et al., *Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.* The New England journal of medicine, 2004. **350**(19): p. 1945-1952.
8. Cooper, J.S., et al., *Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck.* New England Journal of Medicine, 2004. **350**(19): p. 1937-1944+2019.

9. Cooper, J.S., et al., *Long-term follow-up of the RTOG 9501/intergroup phase III trial: Postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck.* International Journal of Radiation Oncology Biology Physics, 2012. **84**(5): p. 1198-1205.
10. Fountzilas, G., et al., *Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: A hellenic cooperative oncology group phase III study.* Medical Oncology, 2004. **21**(2): p. 95-107.
11. Huguenin, P., et al., *Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2004. **22**(23): p. 4665-4673.
12. Ghadjar, P., et al., *Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94).* Int J Radiat Oncol Biol Phys, 2012. **82**(2): p. 524-31.
13. Olasz, L., et al. *Results and failures with or without cisplatin containing induction chemotherapy in the treatment of squamous cell carcinoma of the head and neck*. Cancer detection and prevention, 2004. 65-71 DOI: 10.1016/j.cdp.2003.11.007.
14. Budach, V., et al., *Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: Final results of the Radiotherapy Cooperative Clinical Trials Group of the German Cancer Society 95-06 prospective randomized trial.* Journal of Clinical Oncology, 2005. **23**(6): p. 1125-1135.
15. Ezzat, M., et al., *A randomized study of accelerated fractionation radiotherapy with and without mitomycin C in the treatment of locally advanced head and neck cancer.* Journal of the Egyptian National Cancer Institute, 2005. **17**(2): p. 85-92.
16. Haffty, B.G., et al., *Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: Final results of a randomized clinical trial.* International Journal of Radiation Oncology Biology Physics, 2005. **61**(1): p. 119-128.
17. Hitt, R., et al., *Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer.* Journal of Clinical Oncology, 2005. **23**(34): p. 8636-8645.
18. Mendenhall, W.M., et al., *Radiotherapy alone or combined with carbogen breathing for squamous cell carcinoma of the head and neck: A prospective, randomized trial.* Cancer, 2005. **104**(2): p. 332-337.
19. Sanguineti, G., et al., *Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: Results of a multicenter Phase III study.* International Journal of Radiation Oncology Biology Physics, 2005. **61**(3): p. 762-771.
20. Soo, K.C., et al., *Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison.* British Journal of Cancer, 2005. **93**(3): p. 279-286.

21. Bensadoun, R.J., et al., *French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC).* International Journal of Radiation Oncology Biology Physics, 2006. **64**(4): p. 983-994.
22. Bonner, J.A., et al., *Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.* New England Journal of Medicine, 2006. **354**(6): p. 567-578.
23. Curran, D., et al., *Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab.* Journal of Clinical Oncology, 2007. **25**(16): p. 2191-2197.
24. Bonner, J.A., et al., *Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival.* The lancet oncology, 2010. **11**(1): p. 21-28.
25. Bourhis, J., et al., *Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: A GORTEC trial.* Journal of Clinical Oncology, 2006. **24**(18): p. 2873-2878.
26. Mitra, D., et al., *Chemoradiotherapy for advanced head and neck cancer - Analysis of a prospective, randomized trial.* Indian J Otolaryngol Head Neck Surg, 2006. **58**(4): p. 360-3.
27. Posner, M.R., et al., *Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.* New England Journal of Medicine, 2007. **357**(17): p. 1705-1715.
28. Vermorken, J.B., et al., *Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer.* New England Journal of Medicine, 2007. **357**(17): p. 1695-1704.
29. Van Herpen, C.M.L., et al., *Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323).* British Journal of Cancer, 2010. **103**(8): p. 1173-1181.
30. Argiris, A., et al., *Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer.* The Laryngoscope, 2008. **118**(3): p. 444-449.
31. Ghoshal, S., et al., *Concomitant Boost Radiotherapy Compared with Conventional Radiotherapy in Squamous Cell Carcinoma of the Head and Neck - a Phase III Trial from a Single Institution in India.* CLINICAL ONCOLOGy, 2008. **20**(3): p. 212-220.
32. Racadot, S., et al., *Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement.* Radiotherapy and Oncology, 2008. **87**(2): p. 164-172.
33. Sarkar, S.K., et al., *Comparative study of efficacy and toxicities of cisplatin vs vinorelbine as radiosensitisers in locally advanced head and neck cancer.* The Journal of laryngology and otology, 2008. **122**(2): p. 188-192.

34. Suwinski, R., et al., *Randomized clinical trial on 7-days-a-week postoperative radiotherapy for high-risk squamous cell head and neck cancer.* Radiotherapy and Oncology, 2008. **87**(2): p. 155-163.
35. Gupta, D., et al., *A prospective comparision of sequential chemoradiation vs concurrent chemoradiation in locally advanced oropharyngeal carcinomas.* Cancer biology & therapy, 2009. **8**(3): p. 213-217.
36. Rasch, C.R.N., et al., *Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial.* Cancer, 2010. **116**(9): p. 2159-2165.
37. Ackerstaff, A.H., et al., *First-year quality of life assessment of an intraarterial (radplat) versus intravenous chemoradiation phase III trial.* Head and Neck, 2009. **31**(1): p. 77-84.
38. Ackerstaff, A.H., et al., *Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer.* Head and Neck, 2012. **34**(7): p. 974-980.
39. Grazia Ruo Redda, M., et al., *Radiotherapy alone or with concomitant daily low-dose carboplatin in locally advanced, unresectable head and neck cancer: Definitive results of a phase III study with a follow-up period of up to ten years.* Tumori, 2010. **96**(2): p. 246-253.
40. Rischin, D., et al., *Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. **28**(18): p. 2989-2995.
41. Rodriguez, M.O., et al., *Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck.* Cancer Biology and Therapy, 2010. **9**(5): p. 343-349.
42. Bourhis, J., et al., *Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: Results of a GORTEC randomized trial.* Radiotherapy and Oncology, 2011. **100**(1): p. 56-61.
43. Hamed, R.H. and E. Elzahaf, *Low dose weekly paclitaxel versus low dose weekly cisplatin with concomitant radiation in locally advanced head and neck cancers.* Journal of Cancer Science and Therapy, 2011. **3**(7): p. 168-172.
44. Nutting, C.M., et al., *Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial.* The lancet oncology, 2011. **12**(2): p. 127-136.
45. Quon, H., et al., *Phase III study of radiation therapy with or without Cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: An intergroup trial of the Eastern Cooperative Oncology Group (E2382).* International Journal of Radiation Oncology Biology Physics, 2011. **81**(3): p. 719-725.
46. Zackrisson, B., et al., *Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma--the ARTSCAN study.* Radiother Oncol, 2011. **100**(1): p. 41-8.

47. Bourhis, J., et al., *Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): An open-label phase 3 randomised trial.* The lancet oncology, 2012. **13**(2): p. 145-153.
48. Gupta, T., et al., *Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial.* Radiotherapy and Oncology, 2012. **104**(3): p. 343-348.
49. Halim, A.A.F., et al., *Concomitant chemoradiotherapy using low-dose weekly gemcitabine versus low-dose weekly paclitaxel in locally advanced head and neck squamous cell carcinoma: A phase III study.* Medical Oncology, 2012. **29**(1): p. 279-284.
50. Haddad, R., et al., *Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): A randomised phase 3 trial.* The lancet oncology, 2013. **14**(3): p. 257-264.
51. Skladowski, K., et al., *Radiation-free weekend rescued! Continuous accelerated irradiation of 7-days per week is equal to accelerated fractionation with concomitant boost of 7 fractions in 5-days per week: Report on phase 3 clinical trial in head-and-neck cancer patients.* International Journal of Radiation Oncology Biology Physics, 2013. **85**(3): p. 741-746.

Appendix 4 Outcomes identified in the systematic review

1	Acute salivary gland toxicity (grade 2 or worse)
2	Acute toxicity
3	Cancer-specific survival
4	Cause-specific survival
5	Complete response rate
6	Disease-free survival
7	Disease-specific survival
8	Distant metastases
9	Duration of complete response
10	Duration of response
11	Early death
12	Event free survival
13	Failure-free survival
14	Freedom from distant metastases
15	Gastrostomy tube
16	Hospitalization
17	HR- QOL
18	Identification of parameters that might predict a benefit from carbogen breathing
19	Immunogenicity
20	Influence of variations in dose–volume distributions in targets and critical organ volumes on the outcome regarding both disease and morbidity
21	Laryngeal oedema
22	Late toxicity
23	Local and regional recurrence
24	Local control
25	Local recurrence
26	Local recurrence-free survival
27	Loco-regional control
28	Locoregional progression
29	Locoregional progression-free survival
30	Locoregional recurrence-free survival
31	Metastasis control rates
32	Metastasis-free survival
33	Nutritional toxicity
34	Organ preservation rate
35	Overall control rate
36	Overall Survival
37	Pathological response
38	Patterns of failure
39	Prognostic factors
40	Progression-free survival
41	Recurrence patterns
42	Regional recurrence
43	Relapse
44	Response
45	Safety
46	Second cancer free survival
47	Second primary malignancy
48	Second primary tumours
49	Specific survival
50	Survival benefit
51	Systemic Control
52	Time to distant metastatic relapse
53	Time to locoregional failure
54	Time to progression
55	Time to radical surgery
56	Time to treatment failure
57	Variations in outcome in different sub-sites and stages with respect to treatment type
58	Xerostomia

Appendix 5 Telephone script MDACC

Hello <<participant name>>,

I would like to introduce myself. My name is Aoife Waters and I believe <<Kate Hutcheson>> told you I would call to discuss the research we will be conducting at the MD Anderson?

Before we proceed is this a good time to speak?

If no;

Could you tell me when would be a good time to speak?

<<Make arrangements for further call>>

If yes;

I would like to start off by thanking you for agreeing to speak with me about my research. I understand that <<Kate Hutcheson>> sent you an information leaflet.

Have you had a chance to look at this?

Do you have any questions?

<<Answer any questions about study>>

I also understand that she sent you a copy of the consent form; do you have any questions about any of this?

Taking all of these things into account do you think you would like to go through with the interview?

If no;

Do you mind if I ask if there any particular reasons for not wanting to take part or if there is anything we could have done differently?

Thank you for your time. I would just like to reassure you, as I'm sure <<Kate>> did, that your decision will have absolutely no impact on your follow up or clinical care.

If yes;

Thank you for agreeing to participate in this research, we hope it will help those affected by oropharyngeal cancers. <<Kate>> will be in touch with the details of the time and place for the interview. Before the interview we will go through any further questions you have and ask you to sign a consent form to say you are happy to take part. Please

remember you are free to pull out of the research at any time, without explanation, and this will have no impact on your follow up or clinical care.

If in the meantime you have any questions, please contact <<Kate Hutcheson>> who will answer your question or put you in touch with someone who can.

Thank you for your time, goodbye.

Appendix 6 Interview topic guide

The CONSENSUS Study

Squamous Cell Carcinoma of the Oropharynx: Late Phase Clinical Trial Core Outcomes

Topic Guide for interviewing patients

This topic guide outlines the questions and prompts that may be used during the interviews. This will be adapted as the study proceeds according to the need/preferences of each participant, feedback from The Mersey Head and Neck Cancer Patient and Carer Research Forum and the emerging analysis.

Introduction

I've come to talk to you about what life has been like since your treatment for cancer and your thoughts and feelings on this because what you think is very important to me and my research.

This is my voice recorder so that I can remember what we talk about today - is it OK for me to record?

Everything we talk about today is private, only me and a professional secretary will listen to the recording and when we write about the project we don't mention your name or any place names or anything like that. You don't have to answer all the questions – please tell me if you would like to move on to a different subject.

If you feel uncomfortable while we are talking or you may need a break for a drink or need to go to the toilet, just let me know and we can stop for a while. We are probably going to talk for about an hour and a half. I have plenty time so if it takes longer that's absolutely fine with me, as long as you're happy too.

I will keep my phone here- I need to check in with work at 1pm to tell them where I am.

There are no right or wrong answers– I'm just interested in hearing about your views and experiences.

I'll jot down some note as we go along and refer to the questions but don't be distracted by that.

Do you want to ask me anything before we start?

Main Discussion

General

1. I'd like to get a picture of what life's like for you at the moment, could you tell me a bit about that?
2. How are you getting along at the moment? With regards to…
    a) Are there things that you need help with on a daily basis? What are these? What kind of help do you need? Who helps you with this?
3. Since your diagnosis and treatment has life changed for you? What ways has life changed?
4. Do you still have good days and bad days?
5. What's a good day like for you?
6. What's a day like for you when things are not so good?
7. Are there things you'd like to do since your treatment but can't, could you tell me about that?
8. Some people have said that their sleep has been affected by the treatment; have you found this to be the case? What impact has this had on your life?

Diagnosis

9. Thinking about your feelings around the time that you got diagnosed, how have these changed as time has gone by?
10. On reflecting back now on that time, is there anything you would have changed? i.e. would you have made any different decisions?
11. Did you feel clear about what your options were?
12. Tell me about any symptoms you had prior to starting treatment, how have these changed, if at all?
13. What was/is your relationship like with the clinical team?
14. How do you feel about the care they gave you… did you ever have any doubts about aspects of the care
15. What things helped you through your treatment?
16. Is there anything that you think should have been done or provided to help you during your treatment that wasn't?

Treatment

17. Thinking about your treatment, in general how did you find it?
    a) Was your response to treatment as you expected?

18. When you think about your treatment and the side effects- which were the most difficult side effects of your treatment to deal with?
    a) Which of the side effects that you described are you still having trouble with?
19. Was there any point at which you thought that it wasn't worth it or that the side effects were too much to handle?

    IF HPV-POSITIVE AND AWARE OF THIS

    a) How did you feel when you were told that your cancer was related to a virus?
20. Are there any problems that have arisen that haven't been addressed?

Relationships

21. All relationships have their ups and downs – could you tell me a little about how you get along together?
22. Has your illness and treatment affected your relationships with those close to you? Could you tell me a bit about that?
23. Some people have said that the treatment has had an impact on the physical or intimate side of their relationships. Has it had any impacts on your relationships in this way? [prompt what about your your sex-life – has it affected that side of life?]
24. Has the diagnosis and treatment changed the way you feel about yourself
    a) Mentally and physically

Socialising

25. Tell me about your social life [prompt- has this changed?]
    a) Did you find it difficult to do the things you would usually do? Did that change much during your treatment?
26. What do you like to do in your spare time?
    a) Are you still able to do activities/pastimes that you enjoy?
    b) What are the things that make it easier/harder for you to do these pastimes?
27. Some people have mentioned that they find it difficult to do the sports they used to- have you found this to be the case? [lack of energy or get up and go or mouth dryness being a problem]

Work

28. Have any problems arisen at work linked to your cancer treatment?

Worries and concerns

29. Do you have any particular worries or concerns?
30. What (if anything) helps with dealing with these worries or concerns?
31. How was your mood during your treatment? How is it now?

The Future

32. How do you feel about the future?
33. What would you say your priorities are in life at the moment? What would you have said if I'd asked that question before your illness and treatment?

Other issues

34. As we discussed previously, the purpose of this research is to find out which outcomes of treatment are important and should be measured when we're considering how effective a new treatment is. Today you mentioned difficulties with….. what would you say are the most important outcomes to you, could you list these in order? Are there any other outcomes that you think are important?
35. Is there anything else that is important to you that we haven't talked about today?
36. Is there anything else you'd like to say

……

Closing interview

Thank you for spending time with me today.

[Give out my contact details]

Appendix 7 Patient and carer responses to interview questions, coding and categories

'Since your diagnosis and treatment has life changed for you? What ways has life changed?'

Respondent	How has life changed	Outcome or outcome domain	Delphi question
C3	Erm, no, not really, only cos I've thought I wouldn't let it change you know… obviously me eating and things like that have changed, but I've tried to get everything back going to how it was before.	*Maintaining usual routine* *Difficulty eating and drinking*	*The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)* *The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)* *The long-term impact of a treatment on diet*
C6	I haven't got as much saliva as I did before. My mouth opening, um, I have got a wonky smile, which ((laughs)) which I actually think is quite funny. Um, and, you know, I get, like today, if I feel all here in my shoulders, from the	*Mouth dryness* *Trismus*	*The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment* *The risk of long-term difficulty*

	treatment. It gets stiff at times, and the scar itself can be quite, just stiff, not so much… So you get reminded of it, but it's nothing to what it was.	*Asymmetrical smile* *Shoulder stiffness* *Scar* *Reminders of treatment*	*opening the mouth or of pain in the jaw associated with treatment* *The long term risk of treatments altering a person's physical appearance* *The long-term impact of a treatment on neck and shoulder movement and functioning* *The risk of permanent skin changes associated with treatment (e.g. pigmentation changes, telangiectasia, scarring, acne or photosensitivity)* *Multiple outcomes in this case are reminders, questions related to composite parts, no generic 'reminder of treatment' outcome*
C10	socially it's practically non-existent, um, apart from family. Um, because I can't eat and drink, um, so, er, we hardly, well we hardly go anywhere.	*Social isolation*	*The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or*

	Um, and, um, it's just, it is totally different because I loved eating and I loved drinking wine. I can't eat with other people because it's such a difficult thing. And I certainly can't talk when I'm eating. Um, the rest of it I still do what I used to do before, apart from exercise, because I used to run, um, I used to walk to work, um; I haven't got a job now. I mean, life has changed. Completely. Um ((coughs)) but I still try and do most of the things that I used to do. Um, but my mouth is so dry most of the time.	*Difficulty eating and drinking* *Loss of enjoyment of food* *Socialising with food* *Things going down the wrong way* (triangulated from field notes and comparison with other responses, aspiration if eats/drinks and talks) *Difficulty exercising because of mouth dryness* *Longer-term impact of*	*holidays)* *The long-term effect of a treatment on the ability or desire to eat or drink in public and participate in social occasions that involve food* *The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)* *The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment* *The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)* *The long-term impact of a*

		treatment on ability to return work *Life has changed completely*	*treatment on the ability to return to work* *Multiple outcomes in this case have been life changing, questions related to composite parts, no generic 'life changing' outcome*
C17	I'm on Megace for eating because I can't eat if I don't take Megace. And one of the side effects of Megace is insomnia. So I get up in the mornings and I'm fatigued but I can usually kind of get my act together and go do what I need to do. And I might be fine for 4, 5 hours and it's like I hit a wall and then I just need to go to bed. Or I go to bed and I lay in bed 2 or 3 hours, the frustration for that is I've always been an extremely athletic, active person playing in a tennis league, doing all sorts – I cannot plan to consistently do anything that requires a commitment of my energy and time. Physically can't do it and I'm still in that boat of some fatigue every day, so that's [whispers] REALLY ANNOYING!	*Long term impact of a treatment on appetite* *Difficulty maintaining weight* *Interrupted sleep*	*The long-term impact of a treatment on appetite* *The long-term impact of a treatment on weight and the ability to maintain a steady weight* *The requirement for supportive treatment measures* *The long-term impact of a treatment on sleep (e.g. sleep interruption because of mouth dryness, altered secretions, pain or discomfort in the neck or shoulder or worries or concerns*

		Fatigue	*The risk of long-term fatigue or tiredness associated with treatment*
		Loss of physical strength	*The long-term impact of a treatment on physical strength*
		Purpose	*The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)*

'As we discussed previously, the purpose of this research is to find out which outcomes of treatment are important and should be measured when we're considering how effective a new treatment is. Today you mentioned difficulties with [name outcome(s)] what would you say are the most important outcomes to you, could you list these in order? Are there any other outcomes that you think are important?

Respondent	Outcomes of importance	Outcome or outcome domain	Delphi question
C1	Saliva sucks, swallowing is awkward. Numbness not a big deal, it's just there I mean I touch here and I feel it over there. So if I could rank them saliva. Saliva and fatigue. Those are the two.	Mouth dryness	The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment
		Difficulty swallowing	The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)
		Numbness of skin (Triangulated from field notes, pointed to neck scar)	The risk of long-term numbness of the skin of the ear/neck associated with treatment
		Fatigue	The risk of long-term fatigue or tiredness associated with treatment

C3	The dryness in me mouth is the biggest issue… as I said to you before, when you go out and you're eating in company, you gotta be careful what you eat, that can be a bit embarrassing that's erm… me arm and me shoulder	*Mouth dryness* *Difficulty swallowing* *Socialising with food* *Shoulder stiffness*	The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment *The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)* *The long-term effect of a treatment on the ability or desire to eat or drink in public and participate in social occasions that involve food* *The long-term impact of a treatment on neck and shoulder movement and functioning*
C14	Well I mean to surviving, and to get through, you have got to have nutrients haven't you to sort of like, to make you better. Um, so I am pleased I had the PEG in	*Survival* *PEG*	*How well the treatment prevents death from the cancer* *Some treatments are very toxic and carry a risk of death, how important is it that this risk from*

			treatment is measured? *The effect of a treatment on the need for long-term regular enterostomy tube feeding*
C11	That's the worst bit I think. Talking to you I think my mouth's dried up again. Can you not tell my mouth's, my speech is funny? Well I haven't got any saliva… it means I don't get a good night's sleep. Because when you wake up you imagine when ((coughing)) (inaudible 41.39) and they say people stuck in the desert and their tongue's stuck to their throat and there's dryness everywhere and there's nothing, and that's just what it's like.	*Mouth dryness* *Speech changes* *Interrupted sleep*	The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment *The long-term impact of a treatment on speech and voice* *The long-term impact of a treatment on sleep (e.g. sleep interruption because of mouth dryness, altered secretions, pain or discomfort in the neck or shoulder or worries or concern*

Appendix 8 Patient and carer information sheet (interviews, UK)

Aintree University Hospitals NHS
NHS Foundation Trust

The CONSENSUS Study

Squamous Cell CarcinOma of the OropharyNx:

Late PhaSE CliNical TrialS; Core OUtcomeS

Patient and Carer Interviews

Participant Information Leaflet

CANCER RESEARCH UK | CENTRE OF EXCELLENCE

MRC | Hubs for Trials Methodology Research
North West Hub

You are being invited to take part in a research study

Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and talk to others about the study if you wish.

One of our team will go through the information sheet with you and answer any questions you have. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 tells you the purpose of the study and what will happen if you take part. Part 2 gives you more detailed information about the conduct of the study.

Part 1

What is the purpose of the study?

We are conducting this study because we would like to ask you about your or your partner's experiences of treatment for oropharyngeal cancer. We wish to establish which aspects and side effects of treatments you feel are most important to measure.

We decide which treatments are best by measuring their effect on outcomes like survival and how well the disease is controlled, in clinical trials.

Unfortunately, different trials don't measure the same outcomes so it is hard to compare treatments to decide which is best. Also, outcomes like quality of life and swallowing—which are often quite badly affected by the type of treatment you have had—are often ignored.

We feel that patients, and those involved in the care of patients, should have some say as to which outcomes should be measured in clinical trials for new treatments which is why we are conducting this study.

Who is conducting the research?

Aoife Waters is a clinical research fellow at the University of Liverpool and an Ear, Nose and Throat Doctor. She is conducting this study under the primary supervision of Terry Jones, Professor of Head and Neck Surgery.

Why have I been invited?

You have been approached about this study because you or your partner have had treatment for oropharyngeal cancer.

Do I have to take part?

No, your participation is entirely voluntary.

What will happen to me if I take part?

Aoife would like to spend an hour or so with you discussing your feelings about you or your partner's cancer diagnosis and treatment. There are no right or wrong answers – we are just interested in hearing about your views and experiences. Your responses will be kept confidential, and no members of your clinical team will have access to these.

Aoife will ask you if it's ok to audio-record the interview. You can stop or ask for the recorder to be switched off at any point.

At a later stage you will be asked if you would like to participate in an emailed or postal survey and meeting to decide which are the most important things to be measured in trials of new treatments for oropharyngeal cancer. You are under no obligation to participate in this.

What are the possible risks and benefits of participating?

We hope this study will benefit oropharyngeal cancer patients and their carers in the future by improving the way that we assess medical treatments for this type of cancer. Sometimes people can find it upsetting to talk about difficult experiences. However, we do not have to discuss anything that you don't want to talk about.

What happens next?

If you are interested in participating then we will take your contact details and call you at home in a few days once you've had time to think about the study. At that point we can give you more information, and answer any questions you have about the study. If at this point you feel happy to proceed then arrangements will be made for the interview.

On the day of the interview, Aoife will ask you to sign a consent form. At any point you are still free to withdraw consent even after signing the form. Similarly, further information will be given about the survey and consensus meeting and consent sought closer to the time.

If you express an interest in participating then, with your consent, Aoife will have a look at your medical notes to collect some information about the type of cancer you have had and your treatment. This information will be stored securely and destroyed at the end of the study.

What happens if I change my mind?

You are entitled to withdraw from the study at any point, without explanation, and this will have no impact on your clinical care.

What if there is a problem?

Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Further information on this is given in part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. These details are included in part 2.

Who can I contact for further information?

If you have any questions at all, please contact:

Aoife Waters, University of Liverpool
aoife.waters@liv.ac.uk or 07709451944

Shirley Pringle, Research Practitioner

shirley.pringle@aintree.nhs.uk or 0151 529 5873

or

Professor Terry Jones, University of Liverpool
T.M.Jones@liv.ac.uk or 0151 529 5259

Thank you for reading so far – if you are still interested, please read Part 2.

Part 2

What if I have a complaint?

If you have a concern about any aspect of this study, you should speak to Aoife Waters or Professor Terry Jones who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of this procedure can be obtained from your local hospital. This study is covered for harm due to negligence and non-negligence by the University of Liverpool. Should you have grounds for legal action against the University of Liverpool, you may have to pay your legal costs. NHS complaints mechanisms will also be available to you.

Confidentiality and Data Protection

Only authorized persons will have access to any information about you. The audio-recordings will be marked with a number only. All identifying details will be removed from the records of interviews before these are analyzed by the study team.

All data collected for this study will be kept safely and securely on computer and on typed-up paper records. Professor Terry Jones is the primary supervisor for this study and will be the custodian of all study data.

With your permission, the typed record of your interview (with all identifying details removed) will be stored at the University of Liverpool for up to 10 years in case queries arise and it is necessary to check that the study has been carried out properly. This data may also be used for future research. If you do not wish the typed record of your interview to be stored they will be destroyed at the end of the study. All audio-recordings will be destroyed at the end of the study.

Confidentiality can be guaranteed for the postal survey, however should you choose to participate in the consensus meeting then by nature of its group setting, this cannot be guaranteed.

Publication

The study's results will be published in reports and scientific journals, but it will not be possible to identify any individuals from these reports. We will send you a summary of the results at the end of the study if you would like one.

Who is organising and funding the research?

Aoife Waters is undertaking a PhD studentship and is funded by the Medical Research Council via the University of Liverpool.

Who has reviewed the study?

This study has been reviewed for suitability by the Mersey Head and Neck Cancer Patient and Carer Research Forum.

The study was given a favourable ethical opinion for conduct in the NHS by the Liverpool Central Research Ethics Committee.

Thank you for reading, please ask any questions you may have.

Appendix 9 Patient interview consent (UK)

<<INSERT HOSPITAL HEADER HERE>>

The CONSENSUS Study

Squamous Cell CarcinOma of the OropharyNx: Late PhaSE CliNical TrialS; Core OUtcomeS

Patient consent form: Interview

		Please initial box	
1.	I confirm that I have read and understand the information sheet dated ……. (Version …….) for the CONSENSUS study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.		
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care or legal rights being affected.		
3.	I understand that audio-recordings of my interview will be used for the CONSENSUS study. I understand that brief quotations will be made as part of this study and that nobody will be able to identify any participants in these reports.		
4.	I agree to the typed records of my interview being stored at the University of Liverpool for up to 10 years after the end of this study for checking purposes. I understand that these will be held securely and marked with a number only.		
5.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Liverpool, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical records.		
6.	I understand that the information gathered for this study may be looked at again in the future to help us answer other study questions. If so, an ethics committee will first review the study to ensure the information is used ethically. I give permission for future researchers to have access to this information.		
7.	I would like to receive a summary of the findings at the end of the study.	Yes	No
8.	I agree to take part in the above study.		

Name of participant	Date	Signature
Name of researcher	Date	Signature

When completed, 1 for participant, 1 for researcher's file, 1 original to be kept in medical notes.

Appendix 10 Delphi letter of invitation

[Patient address]

[Date]

Dear [Insert name],

I hope this letter finds you well. It was lovely to speak to you on the phone this afternoon. Following on from our conversation, please find enclosed a copy of the questionnaire that I mentioned along with consent forms.

We have conducted interviews with over thirty patients and carers, both in the UK and the USA and have found out lots about what things are important to people who, like you, have had oropharyngeal cancer. The survey we ask you to complete will help us figure out which are the top most important things to consider when testing out new treatments for oropharyngeal cancer.

I wonder if you would mind having a look at the information sheet, survey and consent form included. If you are happy to complete this could you do so in the next couple of weeks and return the questionnaire to me, along with the signed consent form in the stamped, addressed envelope.

Alternatively you could complete an online version of this survey if you would rather, if this is the case, please email me at aoife.waters@liverpool.ac.uk and I can send you a link to complete the questionnaire online.

If you have any questions at all or would like to discuss anything either before or after completing the questionnaire, please don't hesitate to get in touch at aoife.waters@liverpool.ac.uk or [phone number].

I look forward to hearing from you and thank you again for taking part in this important research that we really hope will improve life for future patients being treated for oropharyngeal cancer.

Best Wishes,

Aoife

Aoife Waters

Clinical Research Fellow

University of Liverpool

Appendix 11 Delphi Patient and carer information sheet

CONSENSUS Delphi Survey – Patient and Carer Information - Paper

We need your help to improve how we do research into treatments for oropharyngeal cancer – please read on for more information about this study

How are healthcare treatments developed?

To decide which treatments are most effective, doctors and researchers must look at the effect treatments have on patients. This is best done in a **research study** known as a **clinical trial**.

In **clinical trials**, treatments are compared by measuring their effects on certain **outcomes** in patients.

For example, in a trial of how well a new cancer treatment works, **'outcomes'** might include:

- *The number of patients the treatment cures*
- *How well the treatment controls spread of the cancer*
- *What impact the treatment has on the patient's quality of life*

What are the challenges in measuring outcomes?

By comparing the outcomes for different treatments, we can see if one is better than the other. We learn which treatment is best by combining the information on outcomes from a number of different trials.

If the same outcomes are measured in all trials, this is easy to do. But if different outcomes are measured in different trials this causes problems. It is like comparing 'apples and pears'.

Unfortunately, different outcomes are often measured in different trials making it difficult to work out which treatment works best!

What is the solution?

We want all trials in oropharyngeal cancer to use the same **main** outcomes. This would make it a lot easier to work out which treatments are best. When a set of main outcomes has been agreed for a health condition, it is called a '**core outcome set**'. If all studies measured and reported all core outcomes, we could

- Bring together all of the studies to get a better understanding of which treatments are best for oropharyngeal cancer
- Avoid the problem of some studies only reporting a selection of the outcomes that have been measured i.e. 'cherry-picking' the best outcomes to report and withholding the bad results

What is the purpose of the CONSENSUS study?

To develop a **'core outcome set'** for oropharyngeal cancer clinical trials.

How are core outcomes agreed upon?

Deciding which outcomes should be core outcomes requires help from different groups of people.

Core outcomes have to be relevant to health professionals, but more importantly, they have to be relevant to patients and carers. Researchers also need to make sure that all these experts – patients, carers and healthcare professionals – agree on the core outcomes.

The **'core outcome set'** will be decided upon in the CONSENSUS study using a **Delphi Survey**. This is a type of anonymous survey with patients and healthcare professionals.

What happens if I take part?

Taking part involves completing a survey on two occasions. You will see a list of different outcomes and be asked to rate how important it is for researchers to measure each of these in clinical trials.

The outcomes were identified by looking at completed clinical trials to see what they measured, and from **interviews with patients and carers** to see what they thought should be measured. You can add any additional outcomes that you think are missing from the list. Once you have completed the survey the results will be analysed by the CONSENSUS study team. **No one else will see your ratings.**

Once the results have been analysed you will be invited to take part in a **second survey**. This will show how you rated the different outcomes compared with the ratings of others who took part.

We expect that people will naturally differ in how they rate different outcomes; there are no right or wrong answers! Using this information we will ask you to reflect on your own view and on the view of the other people who took part. We will then ask you to re-score each item, either sticking with your original score or changing it.

It is **very important** that you complete both surveys – your opinion really matters and cannot be counted if you only complete the first survey. Having said that, you are free to pull out at any time and this will have absolutely no impact on your clinical care.

Who is conducting the research?

Aoife Waters is a researcher at the University of Liverpool and an Ear, Nose and Throat Doctor.

She is conducting the CONSENSUS study with **Terry Jones**, Professor of Head and Neck Surgery, University of Liverpool.

Confidentiality and data protection

When you register, your personal information will be stored securely and not shared with anyone outside the CONSENSUS study team. Only the study team will have access to your ratings. All data collected for this study will be kept safely and securely on computer and on typed-up paper records. Any identifiable information will be destroyed at the end of the study.

With your permission, your ratings will be stored at the University of Liverpool for up to 10 years in case queries arise and it is necessary to check that the study has been carried out properly. This data may also be used for future research. If you do not wish the record of your ratings to be stored they will be destroyed at the end of the study. Please email Aoife Waters if this is the case. Professor Terry Jones is the primary supervisor for this study and will be responsible for all study data.

If you have any questions please contact:

Aoife Waters, University of Liverpool at
aoife.waters@liverpool.ac.uk or [Phone number]
or
Shirley Pringle
Research practitioner, Aintree University Hospital
shirley.pringle@aintree.nhs.uk or [Phone number]

Appendix 12 Delphi patient consent

Aintree University Hospitals NHS
NHS Foundation Trust

Where quality matters

CONSENSUS Study

Squamous Cell CarcinOma of the OropharyNx: Late PhaSE CliNical TrialS; Core OUtcomeS

Patient Consent Form: Delphi Survey

		Please initial box	
1.	I confirm that I have read and understand the information sheet dated ……. (Version …….) for the CONSENSUS study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.		
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care or legal rights being affected.		
3.	I understand that the information gathered for this study may be looked at again in the future to help us answer other study questions. If so, an ethics committee will first review the study to ensure the information is used ethically. I give permission for future researchers to have access to this information.		
4.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Liverpool, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical records.		
5.	I would like to receive a summary of the findings at the end of the study.	Yes	No
6.	I agree to take part in the above study.		

Name of participant	Date	Signature
Name of researcher	Date	Signature

Appendix 13 Delphi round one patient and carer survey

Thank you for agreeing to take part in the CONSENSUS study, we value your contribution

We would like to know which outcomes of treatment you feel are important, and should be measured in clinical trials for **oropharyngeal cancer** to discover which treatments are best.

We appreciate that there are a huge number of **short-term side-effects** that may affect you during treatment and in the weeks to months following treatment, such as neck, mouth and throat burns, bowel upset, loss of taste, difficulty swallowing, fatigue and nausea and vomiting, however these are generally well recorded in studies. Our **main focus** here is to find out about which **long-term outcomes** are important, i.e. those that last for years or even for the rest of your life, although we also ask about short-term effects below.

To find out which outcomes are currently measured and important to patients and carers, we have:

- looked at **previous clinical trials** and
- conducted **interviews** with over 30 patients and carers

When we did this we found the **50 outcomes** listed below. Fifty outcomes would be **too many** for researchers to measure in clinical trials. In order to come up with a smaller list we now want to find out what people think are the top **most important** outcomes to measure. We would like you to:

- read through the list
- consider the question at the start and then
- score the **importance of each outcome** to you

It should take about 15 minutes to complete the survey.

Please remember that there are no right or wrong answers – it is your own opinion that we're interested in.

Even if you have never experienced the outcome, please try and think about how important knowing about this would have been in helping you make a decision about treatment.

There may be **other outcomes** that you think are important. If you would like to add any outcomes to the list **please add them** in the space provided at the **bottom of the page**.

We have used plain English to describe outcomes with the medical language version *in italics* below, (if one exists). For some of the outcomes you can see a further explanation.

Please provide the following details in order for us to contact you about the 2nd round of the survey

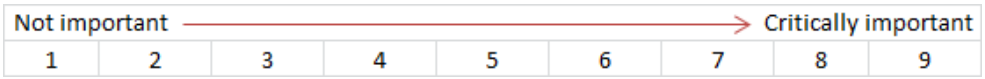
Title	
Name	
Email address (or home address if you would like to complete a paper copy)	
Phone number	
Type of treatment	
Date treatment ended	

CONSENSUS Delphi Survey

Please score all outcomes using the scoring system below. You may have no experience of many of the outcomes however we ask that you score how important you think these would be in helping you to **decide between treatments**.

Scores range from **not important** (1) to **critically important** (9). Shade the box that you feel is appropriate. If you feel unable to comment, please select **'Unable to score'.**

Scoring system



Outcome	Importance									
	Not important			Important but not critical			Critical			Unable to score
	1	2	3	4	5	6	7	8	9	
	You are not concerned if this is measured in clinical trials			This is important but it is not critical that it is measured in clinical trials			This should be measured in clinical trials			
	○	○	○	○	○	○	○	○	○	○

If you are unsure about what to do please contact aoife.waters@liverpool.ac.uk or [Phone number].

CONSENSUS Delphi Survey

How important is it, on a scale of 1-9, that we measure the following outcomes in clinical trials of treatments for oropharyngeal cancer?

Number	Terminology	Outcome	Importance									
			Not important			Important but not critical			Critical			Unable to score
			1	2	3	4	5	6	7	8	9	
11	Plain English term	**The risk and severity of early side-effects associated with a treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	There are a huge number of short-term side-effects associated with treatment, how important are these in helping people to decide between treatments?										
	Medical term	*The incidence and severity of early side-effects associated with a treatment (e.g. acute toxicities or complications)*										
12	Plain English term	**Having to go into hospital to help deal with side-effects during treatment or when recovering from treatment**	○	○	○	○	○	○	○	○	○	○
13	Plain English term	**The effect of a treatment on a person's ability to carry out their own personal care (e.g. washing, dressing, meal preparation)**	○	○	○	○	○	○	○	○	○	○
14	Plain English term	**The long term risk of treatments altering how a person looks**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that their appearance is altered following treatment, they may have lost weight, their neck may be thinner or they may have scars, one shoulder may sit lower than the other or they may have a facial droop										
	Medical term	*The long-term risk of altered cosmesis, physical deformity or disfigurement associated with treatment*										
15	Plain English term	**The long-term impact of a treatment on hair growth**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people notice that their hair grows back thinner or a slightly different colour following treatment										
16	Plain English term	**The risk of permanent skin changes associated with treatment (e.g. redness or altered colour, broken veins, scarring, acne, increased sensitivity to the sun)**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of permanent skin changes associated with treatment (e.g. pigmentation changes, telangiectasia, scarring, acne or photosensitivity)*										
17	Plain English term	**The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)*										
18	Plain English term	**The effect of a treatment on the need for long-term regular tube feeding**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people need long-term feeding through a tube in the nose or stomach wall following treatment										
	Medical term	*The effect of a treatment on the need for long-term regular enterostomy tube feeding*										
19	Plain English term	**The long-term effect of a treatment on being able to/ wanting to eat or drink in public and take part in social occasions involving food**	○	○	○	○	○	○	○	○	○	○

Number	Terminology	Outcome	Importance									
			Not important			Important but not critical			Critical			Unable to score
			1	2	3	4	5	6	7	8	9	
20	Plain English term	**The long-term impact of a treatment on appetite**	○	○	○	○	○	○	○	○	○	○
	Explanation	Wanting to eat the same amount as before treatment										
21	Plain English term	**The long-term impact of a treatment on diet**	○	○	○	○	○	○	○	○	○	○
	Explanation	Being able to eat and drink the same things as a person did before treatment										
22	Plain English term	**The long-term impact of a treatment on a person's enjoyment of food**	○	○	○	○	○	○	○	○	○	○
23	Plain English term	**The risk of long-term problems with mouth ulcers associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of long-term problems with oral ulcers associated with treatment*										
24	Plain English term	**The long-term effect of a treatment on the ability to breath normally**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes a person requires a tracheostomy or other surgery to help them breathe following treatment										
25	Plain English term	**The risk of long-term mouth dryness and thicker secretions/saliva associated with a treatment**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of long-term xerostomia and altered secretions associated with a treatment*										
26	Plain English term	**The risk of long-term infection in the jaw bone associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people can suffer from chronic infection and poor healing in the jaw bone that may require surgery										
	Medical term	*The risk of osteoradionecrosis associated with treatment*										
27	Plain English term	**The risk of long-term difficulty opening the mouth or of pain in the jaw associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of long-term trismus or pain in the jaw associated with treatment*										
28	Plain English term	**The long-term impact of a treatment on tongue movement**	○	○	○	○	○	○	○	○	○	○
29	Plain English term	**The long-term impact of a treatment on speech and voice**	○	○	○	○	○	○	○	○	○	○
30	Plain English term	**The long-term impact of a treatment on sensation in the mouth and throat**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that they are very sensitive to certain textures, flavours, spices, fizzy drinks and alcohol following treatment										

Number	Terminology	Outcome	Importance									
			Not important			Important but not critical			Critical			Unable to score
			1	2	3	4	5	6	7	8	9	
31	Plain English term	**The long-term impact of a treatment on the skin that lines the mouth**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that the skin lining the mouth is very sensitive following treatment and can become damaged very easily e.g. by eating a crispy baguette										
	Medical term	*The long-term impact of a treatment on the integrity of the oral mucosa and lips*										
32	Plain English term	**The long-term effect of a treatment on taste**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that their sense of taste never returns to normal										
33	Plain English term	**The risk of long-term fatigue or tiredness associated with treatment**	○	○	○	○	○	○	○	○	○	○
34	Plain English term	**The long-term impact of a treatment on physical strength**	○	○	○	○	○	○	○	○	○	○
35	Plain English term	**The long-term impact of a treatment on neck and shoulder movement and functioning**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that they have stiffness of the neck and/or shoulder following treatment, this may give rise to weakness in the shoulder and/or difficulty using the arm										
36	Plain English term	**The long-term impact of a treatment on weight and the ability to maintain a steady weight**	○	○	○	○	○	○	○	○	○	○
37	Plain English term	**The risk of long-term indigestion associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes people find that they get heartburn or that food doesn't agree with them										
38	Plain English term	**The risk of long-term ear problems associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sometimes treatments can cause fluid to build up in the ear which may occasionally lead to discomfort or pain, ear infections or hearing difficulties										
	Medical term	*The risk of long-term Eustachian tube dysfunction associated with treatment (causing glue ear +/- hearing difficulties)*										
39	Plain English term	**The risk of permanent damage to the nerves which can lead to numbness and tingling, burning, stabbing or shooting pains in the hands or to hearing loss**	○	○	○	○	○	○	○	○	○	○
	Medical term	*The risk of long-term neurotoxicity (peripheral neuropathy and ototoxicity) associated with treatment*										
40	Plain English term	**The long-term impact of a treatment on eyesight**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people find that their eyesight fluctuates a lot during and after treatment										

Number	Terminology	Outcome	Importance									Unable to score
			Not important			Important but not critical			Critical			
			1	2	3	4	5	6	7	8	9	
41	Plain English term	**The long-term effect of a treatment on memory and cognition**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people find that their memory is poorer and that they have more difficulty taking information on board or organising their thoughts										
42	Plain English term	**The long-term impact of a treatment on psychological well-being**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people find that their mood can be quite low or they can be depressed, or they can become more anxious or emotional or find that they are more short-tempered/irritable										
43	Plain English term	**The long-term impact of treatment on sleep**	○	○	○	○	○	○	○	○	○	○
	Explanation	Sleep interruption because of mouth dryness, altered secretions, pain or discomfort in the neck or shoulder or because of worries or concerns										
44	Plain English term	**The risk of long-term neck swelling associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people find that fluid builds up in the neck following treatment as it does not drain normally										
	Medical term	*The risk of long-term cervical lymphoedema associated with treatment*										
45	Plain English term	**The risk of long-term numbness of the skin of the ear/neck associated with treatment**	○	○	○	○	○	○	○	○	○	○
46	Plain English term	**The risk of long-term hypothyroidism associated with treatment**	○	○	○	○	○	○	○	○	○	○
	Explanation	Following treatment the thyroid gland sometimes doesn't work as well, this can make a person feel that their energy levels are very low										
47	Plain English term	**The long-term impact of a treatment on body temperature**	○	○	○	○	○	○	○	○	○	○
	Explanation	Some people find that they can be either too hot or too cold and have difficulty controlling their body temperature following treatment										
	Medical term	*The long-term impact of a treatment on thermoregulation*										
48	Plain English term	**The long-term impact of a treatment on the ability to return to work**	○	○	○	○	○	○	○	○	○	○
49	Plain English term	**The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)**	○	○	○	○	○	○	○	○	○	○
50	Plain English term	**The long-term impact of a treatment on relationships (e.g. emotional, physical and sexual relationship with spouse or partner and relationships with other people)**	○	○	○	○	○	○	○	○	○	○

Additional outcomes

If there are **other outcomes** that you feel are important and missing from this list, **please add** them in the **box below** and **score their importance** on a scale of 1-9.

Outcome	Importance									
	Not important			Important but not critical			Critical			Unable
	1	2	3	4	5	6	7	8	9	to score
	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○
	○	○	○	○	○	○	○	○	○	○

Other comments

Thank you for completing the survey. We will contact you by **email or post** in the next 6 weeks or so to complete the **second survey**. We ask that you return this **as soon as possible.**

Please note it is **very important** that you complete both rounds - your opinion really matters and cannot be counted if you only complete the first questionnaire. Having said that, you are free to pull out at any time and this will have absolutely **no impact** on your clinical care.

Please return the completed questionnaire in the stamped, addressed envelope to:

Dr Aoife Waters
Department of Biostatistics
University of Liverpool
1st floor Duncan Building
Daulby Street
Liverpool, L69 3GA
If you have any questions at all, please contact aoife.waters@liverpool.ac.uk or [Phone number].

Appendix 14 Delphi patient and carer email invitation

Dear [Insert name],

You are invited to participate in a 15-minute online survey as part of the CONSENSUS study

- You have been contacted about this survey because you have had or are close to someone who has been treated for oropharyngeal cancer (cancer of the tonsil, tongue base or soft palate)

- **We would like to survey your opinions about which outcomes matter and should be measured in clinical trials of new treatments for oropharyngeal cancer. Your opinions will help us to improve clinical trials on oropharyngeal cancer**

- If you would like to take part in the survey or find out more about it, please follow the link [Insert link] and register. You will find more information about the CONSENSUS study and will be able to complete the survey

You can find more information about outcomes and similar research at the COMET initiative website www.comet-initiative.org

If you have any questions please contact Aoife Waters or Professor Terry Jones at aoife.waters@liverpool.ac.uk or T.M.Jones@liverpool.ac.uk

Many thanks in advance for your contribution to this important research.

Best Wishes,
Aoife
Aoife M I Waters MRCS DOHNS
Clinical Research Fellow
North West Hub for Trials Methodology Research
University of Liverpool

On behalf of the CONSENSUS Study Team (Drs Aoife Waters and Catrin Tudur-Smith and Professors Bridget Young and Terry Jones)

Appendix 15 Development of Delphi Survey

Comprehensive outcomes list	Relates to Delphi question (number)	Delphi Survey (Round 1)
Acute toxicity	11	1. The effect of a treatment on controlling local disease recurrence *How well the treatment stops the cancer coming back in the same place e.g. tonsil, tongue base* 2. The effect of a treatment on controlling regional disease recurrence *How well the treatment stops the cancer coming back in the lymph nodes in the neck* 3. The effect of a treatment on controlling distant disease recurrence *How well the treatment stops the cancer coming back in other parts of the body e.g. lungs, brain, liver* 4. The effect of a treatment in preventing death from cancer *How well the treatment prevents death from the cancer* 5. The risk of death from treatment *Some treatments are very toxic and carry a risk of death, how important is it that this risk **from treatment** is measured?* 6. The effect of a treatment on the risk of death from any cause 7. The effect of a treatment on health-related quality of life *The impact of a treatment on a person's general quality of life* 8. The requirement for dental extractions in the course of treatment *The requirement for unhealthy teeth to be removed in the course of treatment*
Altered diet	11,21	
Altered secretions	11	
Altered sensation in throat	30	
Altered taste	32	
Angular stomatitis	16	
Anxieties/ concerns	42	
Aspiration	17	
Asymmetrical smile	14	
Avoiding oral sex because of HPV	50	
Bad breath	25	
Being able to care for yourself	13	
Being able to look after children	49	
Bowel upset	11	
Cancer spreading	4	

Cataracts	40	9. The requirement for supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy) *The need for additional treatments to get a person through the cancer treatment e.g. pain killers, antibiotics, tube feeding, tracheostomy*
Cough	4	10. The need for additional surgery or invasive procedures as a consequence of treatment (e.g. pharyngeal dilatations, further reconstructive surgery) *The need for additional surgery or invasive procedures as a consequence of treatment (e.g. throat stretches, further surgery to treat complications)*
Death from treatment	25	11. The risk and severity of early side-effects associated with a treatment (e.g. acute toxicities or complications) *The risk and severity of early side-effects associated with a treatment* (There are a huge number of short-term side-effects associated with treatment, how important are these in helping people to decide between treatments?)
Dehydration	5	12. The need for hospitalisation to help deal with side-effects during treatment or recovery from treatment
Dental extractions	11	13. The effect of a treatment on a person's ability to carry out their own personal care (e.g. washing, dressing, meal preparation)
Depression	8	14. The long-term risk of altered cosmesis, physical deformity or disfigurement associated with treatment *The long term risk of treatments altering a person's physical appearance* *(Sometimes people find that their appearance is altered following treatment, they may have lost weight, their neck may be thinner or they may have scars, the shoulder may sit lower than the other or they may have a facial droop)*
Difficult recalling words	42	15. The long-term impact of a treatment on hair growth
Difficulty breaking up food	41	
Difficulty breathing	8, 25,27,28	
Difficulty controlling blood sugars	11,24	
Difficulty eating and drinking	17	
Difficulty exercising because of fatigue	17	
Difficulty exercising because of mouth	33,49	

dryness		
Difficulty maintaining weight	25,49	(Some people notice that their hair grows back thinner or a slightly different colour following treatment)
Difficulty swallowing	36	16. The risk of permanent skin changes associated with treatment (e.g. pigmentation changes, telangiectasia, scarring, acne or photosensitivity)
Disease-free survival	1,2,3,4	*The risk of permanent skin changes associated with treatment (e.g. redness or altered colour, broken veins, scarring, acne, increased sensitivity to the sun)*
Disease-specific survival	4	17. The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)
Early death	5	*The risk of long-term difficulty swallowing associated with treatment (e.g. difficulties with getting food down, or food going up or down the wrong way)*
Emotional relationship with partner	50	18. The effect of a treatment on the need for long-term regular enterostomy tube feeding
Event free survival	1,2,3,4,5,6	*The effect of a treatment on the need for long-term regular tube feeding*
Fatigue	11,33	(Sometimes people need long-term feeding through a tube in the stomach wall following treatment)
Feeling dizzy	11	19. The long-term effect of a treatment on the ability or desire to eat or drink in public and participate in social occasions that involve food
Feeling ill	11	20. The long-term impact of a treatment on appetite
Fluctuating vision	40	(Having the desire to eat the same amount as before treatment)
Food coming up later	17	21. The long-term impact of a treatment on diet
Food intolerance	11,30	(The ability to eat and drink the same things as a person did before treatment)
Food sticking	17	22. The long-term impact of a treatment on the enjoyment of food
Gastrostomy tube	11,18	23. The risk of long-term problems with oral ulcers associated with

		treatment
Glue ear	38	*The risk of long-term problems with mouth ulcers associated with treatment*
Hair loss	11,15	24. The long-term effect of a treatment on the ability to breath independently
Having blood taken	9,10	(Sometimes a person requires a tracheostomy or other surgery to help them breathe following treatment)
Heightened sensitivity in mouth	11	25. The risk of long-term xerostomia and altered secretions associated with a treatment
Hospitalisation for symptom control	12	*The risk of long-term mouth dryness and thickened secretions/saliva associated with a treatment*
Hospitalization	12	26. The risk of long-term osteoradionecrosis associated with treatment
HR- QOL	7	*The risk of long-term infection in the jaw bone associated with treatment*
Hypothyroidism	46	(Sometimes people can suffer from chronic infection and poor healing in the jaw bone that may require surgery)
Impact on carer	50	27. The risk of long-term trismus or pain in the jaw associated with treatment
Interrupted sleep	43	*The risk of long-term difficulty opening the mouth or of pain in the jaw associated with treatment*
Jaw ache	27	28. The long-term impact of a treatment on tongue movement
Lack of appetite	11, 20	29. The long-term impact of a treatment on speech and voice
Lack of motivation	33	30. The long-term impact of a treatment on sensation in the mouth and throat
Laryngeal oedema	11	(Sometimes people find that they are very sensitive to certain textures, flavours, spices, fizzy drinks and alcohol following treatment)
Late toxicity	7,10,14-47	31. The long-term impact of a treatment on the integrity of the oral mucosa and lips
Less patient	42	*The long-term impact of a treatment on the skin that lines the*

		mouth (Sometimes people find that the skin lining the mouth is very sensitive following treatment and can become damaged very easily e.g. by eating a crispy baguette)
Less sex with partner	50	
Less strength in jaw to chew	27	32. The long-term effect of a treatment on taste
Life has changed completely	49	(Sometimes people find that their sense of taste never returns to normal)
Local and regional recurrence	1,2	33. The risk of long-term fatigue or tiredness associated with treatment
Local control	1	34. The long-term impact of a treatment on physical strength
Loco-regional control	1,2	35. The long-term impact of a treatment on neck and shoulder movement and functioning
Locoregional progression	1,2	(Sometimes people find that they have stiffness of the neck and/or shoulder following treatment, this may give rise to weakness in the shoulder and/or difficulty using the arm)
Locoregional recurrence-free survival	1,2	36. The long-term impact of a treatment on weight and the ability to maintain a steady weight
Longer-term impact of treatment on ability to return work	48	37. The risk of long-term indigestion associated with treatment
Longterm oral ulcers	23	(Sometimes people find that they get heartburn or that food doesn't agree with them)
Long-term skin changes	16	38. The risk of long-term Eustachian tube dysfunction associated with treatment (causing glue ear +/- hearing difficulties)
Loss of confidence	42	*The risk of long-term ear problems associated with treatment*
Loss of earnings	48	(Sometimes treatments can cause fluid to build up in the ear which may occasionally lead to discomfort or pain, ear infections or hearing difficulties)
Loss of enjoyment of food	22	39. The risk of long-term neurotoxicity (peripheral neuropathy and ototoxicity) associated with treatment
Loss of libido	50	*The risk of permanent damage to the nerves which can lead to numbness and tingling, burning, stabbing or shooting pains in the*

		hands or to hearing loss
Loss of physical strength	34	40. The long-term impact of a treatment on eyesight
Low mood	42	(Some people find that their eyesight fluctuates a lot during and after treatment)
Lymphoedema	44	41. The long-term effect of a treatment on memory and cognition
Maintaining usual routine	48,49	(Some people have found that their memory is poorer and that they have more difficulty taking information on board or organising their thoughts)
Medication to counter medication	9	42. The long-term impact of a treatment on psychological well-being
Metastases	3	(Some people find that their mood can be quite low or they can be depressed, or they can become more anxious or emotional or find that they are more short-tempered/irritable)
More difficulty organising tasks	41	43. The long-term impact of a treatment on sleep (e.g. sleep interruption because of mouth dryness, altered secretions, pain or discomfort in the neck or shoulder or worries or concerns)
More easily agitated	42	44. The risk of long-term cervical lymphoedema associated with treatment
More emotional	42	*The risk of long-term neck swelling associated with treatment*
More sensitive to the cold	47	(Some people find that fluid builds up in the neck following treatment as it does not drain normally)
Mouth dryness	11,25	45. The risk of long-term numbness of the skin of the ear/neck associated with treatment
Mouth surface raw	31	46. The risk of long-term hypothyroidism associated with treatment
Mucositis	11	(Following treatment the thyroid gland sometimes doesn't work as well, this can make a person feel that their energy levels are very low)
Nasal regurgitation	17	47. The long-term impact of a treatment on thermoregulation
Nausea and vomiting	11	*The long-term impact of a treatment on body temperature*

Neck discomfort	35	(Some people find that they can be either too hot or too cold and have difficulty controlling their body temperature following treatment) 48. The long-term impact of a treatment on the ability to return to work 49. The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays) 50. The long-term impact of a treatment on relationships (e.g. emotional, physical and sexual relationship with spouse or partner and relationships with others)
Neutropenic sepsis	11	
NG feeding/ drinking shakes	9	
Numbness ear/face	45	
Nutritional toxicity	11	
Oesophageal stricture	10,17	
Opioid dependance	9	
Oral candida	11	
Oral hygiene	25	
Oral pain	11	
Organ preservation rate	17,25	
Osteoradionecrosis	26	
Overall control rate	6	
Overall Survival	6	
Passing HPV on to partner	50	
Pathological response	1,2	
PEG	18	
Poorer concentration	41	
Poorer healing	16	
Poorer memory	41	
Progression-free survival	1,2,3,4	
Purpose	49	
Quality of life	7	

Radiation dermatitis	11
Recurrence	1,2,3,4
Reduced oral intake	11
Reflux	37
Regional recurrence	2
Relapse	1,2,3
Reminders of treatment	10,14,16
Response	1,2,3
Scar	14, 16
Shoulder ache	35
Shoulder asymmetry	14,35
Shoulder weakness	35
Smell of tumour breakdown	11
SNHL	11,39
Social isolation	11,50
Socialising	49,50
Socialising with food	19
Speaking exhausting	25
Speech changes	29
Spottier skin	16
Suicidal ideation	11
Support from others	50
Surgical clips	11
Survival	4,5,6
Taking a long time to eat	17
Things going down the wrong way	17
Thinner hair	14
Thread veins	16
Throat discomfort	30
Throat feels smaller	30

Time to progression	1,2,3
Time to treatment failure	1,2,3,4
Tongue protrusion reduced	28
Tracheostomy	11,24
Treatment not being invasive	10
Trismus	27
Voice deeper	29
Voice quieter	29
Weight loss	11,14,36
Wound dehisence	11
Wrinkles	16
Mouth dryness	25

Appendix 16 Distribution of scores for all outcomes

	Panel 1			Panel 2			Panel 3			Panel 3 Clinicians			Panel 3 Patients		
Outcome	1-3%	4-6%	7-9%	1-3%	4-6%	7-9%	1-3%	4-6%	7-9%	1-3%5	4-6%6	7-9%7	1-3%52	4-6%63	7-9%74
Having to go into hospital to help deal with side-effects during treatment or when recovering from treatment	0.0	73.9	26.1	0.0	55.2	44.8	0.0	57.1	42.9	0.0	57.1	42.9	0.0	57.1	42.9
The effect of a treatment in preventing death from cancer	0.0	0.0	100.0	6.9	51.7	41.4	3.6	35.7	60.7	0.0	0.0	100.0	7.1	71.4	21.4
The effect of a treatment on a person's ability to carry out their own personal care (e.g. washing, dressing, meal preparation)	8.7	52.2	39.1	0.0	3.4	96.6	0.0	28.6	71.4	0.0	57.1	42.9	0.0	0.0	100.0
The effect of a treatment on controlling distant disease	0.0	8.7	91.3	0.0	0.0	100.0	0.0	7.1	89.3	0.0	14.3	85.7	0.0	0.0	92.9
The effect of a treatment on controlling local disease	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0
The effect of a treatment on controlling regional disease	0.0	0.0	100.0	0.0	0.0	100.0	0.0	7.1	92.9	0.0	14.3	85.7	0.0	0.0	100.0
The effect of a treatment on health-related quality of life	0.0	26.1	73.9	0.0	31.0	69.0	0.0	14.3	85.7	0.0	7.1	92.9	0.0	21.4	78.6
The effect of a treatment on the need for long-term regular enterostomy tube feeding	0.0	17.4	82.6	3.4	17.2	79.3	0.0	14.3	82.1	0.0	7.1	92.9	0.0	21.4	71.4
The effect of a treatment on the risk of death from any cause	4.3	39.1	52.2	0.0	10.3	89.7	7.1	10.7	82.1	14.3	14.3	71.4	0.0	7.1	92.9
The incidence and severity of early side-effects associated with a treatment (e.g. acute toxicities or complications)	4.3	43.5	52.2	0.0	41.4	58.6	0.0	42.9	53.6	0.0	28.6	71.4	0.0	57.1	35.7
The long-term effect of a treatment on being able to/ wanting to eat or drink in public and take part in social occasions involving food	0.0	39.1	56.5	3.4	34.5	62.1	0.0	32.1	57.1	0.0	50.0	50.0	0.0	14.3	64.3
The long-term effect of a treatment on memory and cognition	8.7	56.5	34.8	0.0	17.2	82.8	3.6	32.1	64.3	7.1	57.1	35.7	0.0	7.1	92.9
The long-term effect of a treatment on taste	0.0	69.6	30.4	0.0	24.1	72.4	0.0	42.9	57.1	0.0	71.4	28.6	0.0	14.3	85.7
The long-term effect of a treatment on the ability to breath normally	4.3	26.1	69.6	6.9	37.9	51.7	0.0	28.6	64.3	0.0	14.3	85.7	0.0	42.9	42.9
The long-term impact of a treatment on appetite	13.0	60.9	26.1	0.0	27.6	72.4	0.0	53.6	42.9	0.0	64.3	35.7	0.0	42.9	50.0
The long-term impact of a treatment on diet	4.3	65.2	30.4	6.9	44.8	48.3	3.6	50.0	46.4	0.0	57.1	42.9	7.1	42.9	50.0
The long-term impact of a treatment on eyesight	8.7	52.2	39.1	0.0	31.0	69.0	3.6	39.3	57.1	7.1	50.0	42.9	0.0	28.6	71.4
The long-term impact of a treatment on hair growth	30.4	56.5	13.0	10.3	48.3	41.4	21.4	60.7	17.9	35.7	64.3	0.0	7.1	57.1	35.7
The long-term impact of a treatment on neck and shoulder movement and functioning	8.7	65.2	26.1	24.1	31.0	44.8	10.7	64.3	25.0	0.0	71.4	28.6	21.4	57.1	21.4
The long-term impact of a treatment on physical strength	17.4	56.5	26.1	20.7	51.7	27.6	10.7	71.4	17.9	7.1	78.6	14.3	14.3	64.3	21.4
The long-term impact of a treatment on psychological well-being	4.3	52.2	43.5	17.2	37.9	44.8	7.1	50.0	35.7	0.0	57.1	42.9	14.3	42.9	28.6
The long-term impact of a treatment on relationships (e.g. emotional, physical and sexual relationship with spouse or partner and relationships with other people)	4.3	52.2	43.5	0.0	27.6	72.4	10.7	57.1	28.6	0.0	64.3	35.7	21.4	50.0	21.4
The long-term impact of a treatment on sensation in the mouth and throat	8.7	56.5	34.8	34.5	41.4	24.1	0.0	64.3	35.7	0.0	71.4	28.6	0.0	57.1	42.9
The long-term impact of a treatment on sleep	21.7	56.5	21.7	0.0	44.8	55.2	0.0	71.4	28.6	0.0	78.6	21.4	0.0	64.3	35.7
The long-term impact of a treatment on speech and voice	0.0	43.5	56.5	6.9	37.9	55.2	0.0	39.3	60.7	0.0	35.7	64.3	0.0	42.9	57.1
The long-term impact of a treatment on the ability to carry out normal activities (e.g. hobbies, exercise, socialising or holidays)	4.3	52.2	43.5	3.4	37.9	58.6	3.6	35.7	60.7	7.1	42.9	50.0	0.0	28.6	71.4
The long-term impact of a treatment on the ability to return to work	4.3	52.2	43.5	0.0	31.0	69.0	7.1	35.7	57.1	0.0	42.9	57.1	14.3	28.6	57.1
The long-term impact of a treatment on the enjoyment of food	4.3	52.2	43.5	6.9	48.3	44.8	10.7	50.0	39.3	7.1	50.0	42.9	14.3	50.0	35.7
The long-term impact of a treatment on the integrity of the oral mucosa and lips	8.7	69.6	21.7	3.4	48.3	48.3	7.1	53.6	39.3	0.0	71.4	28.6	14.3	35.7	50.0
The long-term impact of a treatment on thermoregulation	21.7	73.9	0.0	10.3	37.9	51.7	17.9	46.4	32.1	28.6	64.3	7.1	7.1	28.6	57.1
The long-term impact of a treatment on tongue movement	0.0	56.5	43.5	3.4	37.9	58.6	0.0	50.0	50.0	0.0	57.1	42.9	0.0	42.9	57.1
The long-term impact of a treatment on weight and the ability to maintain a steady weight	0.0	60.9	39.1	3.4	27.6	69.0	0.0	60.7	35.7	0.0	64.3	35.7	0.0	57.1	35.7
The long-term risk of altered cosmesis, physical deformity or disfigurement associated with treatment	0.0	47.8	52.2	3.4	17.2	72.4	7.1	53.6	39.3	0.0	57.1	42.9	14.3	50.0	35.7
The need for additional surgery or invasive procedures as a consequence of treatment (e.g. Tracheostomy, dilatations, further reconstructive surgery)	0.0	34.8	65.2	3.4	37.9	58.6	3.6	32.1	64.3	0.0	42.9	57.1	7.1	21.4	71.4
The requirement for dental extractions in the course of treatment	8.7	65.2	26.1	17.2	37.9	41.4	7.1	67.9	21.4	7.1	78.6	14.3	7.1	57.1	28.6
The requirement for supportive treatment measures (e.g. analgesics, antibiotics, feeding enterostomy, tracheostomy)	0.0	56.5	43.5	6.9	48.3	44.8	0.0	50.0	46.4	0.0	64.3	35.7	0.0	35.7	57.1
The risk of death from treatment	0.0	13.0	82.6	3.4	41.4	55.2	0.0	35.7	64.3	0.0	7.1	92.9	0.0	64.3	35.7
The risk of long-term cervical lymphoedema associated with treatment	17.4	56.5	26.1	0.0	41.4	58.6	3.6	39.3	53.6	0.0	57.1	42.9	7.1	21.4	64.3
The risk of long-term dysphagia associated with treatment (e.g. difficulties with propulsion of food, nasal regurgitation, aspiration or pharyngeal stenosis)	0.0	21.7	78.3	0.0	34.5	65.5	0.0	21.4	78.6	0.0	7.1	92.9	0.0	35.7	64.3
The risk of long-term Eustachian tube dysfunction associated with treatment (causing glue ear +/- hearing difficulties)	26.1	65.2	8.7	3.4	55.2	37.9	17.9	67.9	7.1	14.3	78.6	7.1	21.4	57.1	7.1
The risk of long-term fatigue or tiredness associated with treatment	4.3	69.6	26.1	6.9	37.9	55.2	3.6	57.1	39.3	0.0	71.4	28.6	7.1	42.9	50.0
The risk of long-term hypothyroidism associated with treatment	17.4	69.6	13.0	10.3	37.9	51.7	17.9	64.3	17.9	21.4	71.4	7.1	14.3	57.1	28.6
The risk of long-term indigestion associated with treatment	30.4	60.9	8.7	20.7	44.8	34.5	21.4	53.6	25.0	28.6	57.1	14.3	14.3	50.0	35.7
The risk of long-term neurotoxicity (peripheral neuropathy and ototoxicity) associated with treatment	0.0	65.2	34.8	0.0	27.6	72.4	0.0	50.0	46.4	0.0	64.3	35.7	0.0	35.7	57.1